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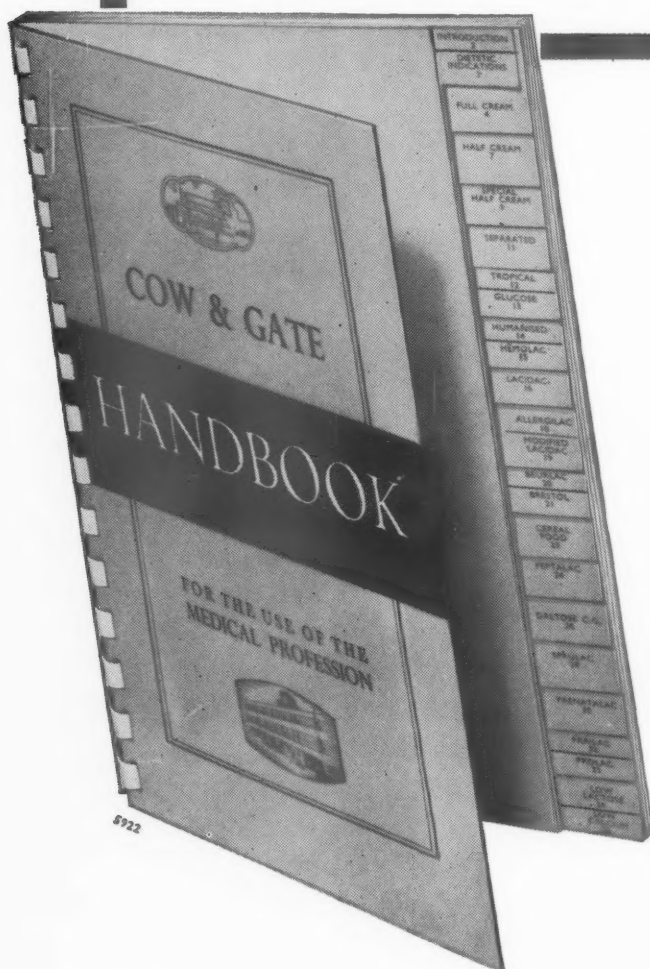
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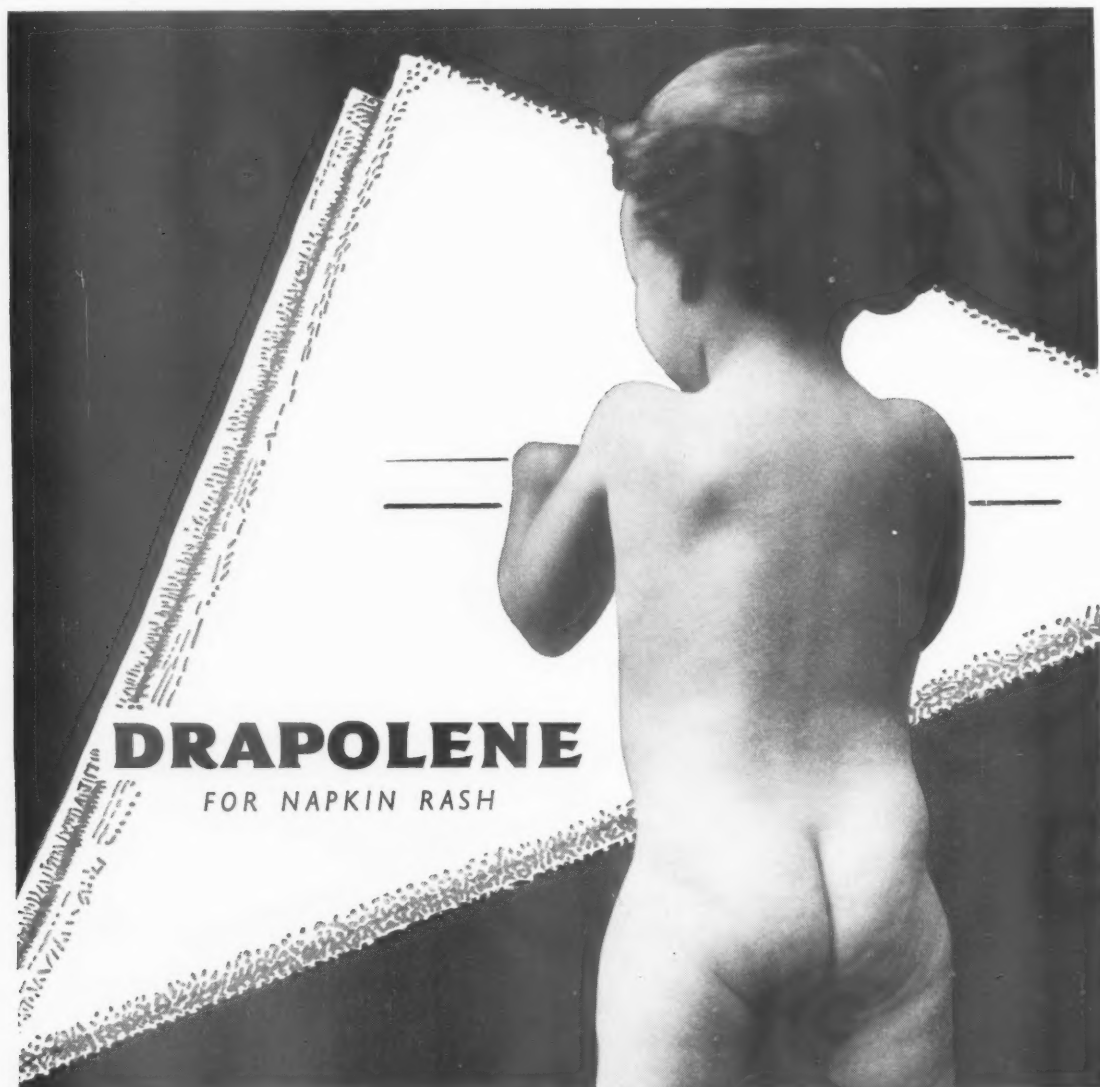
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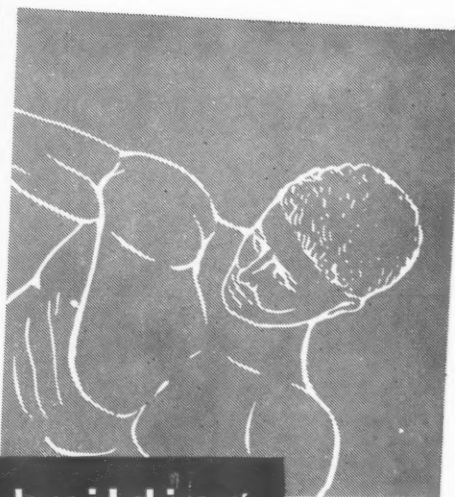
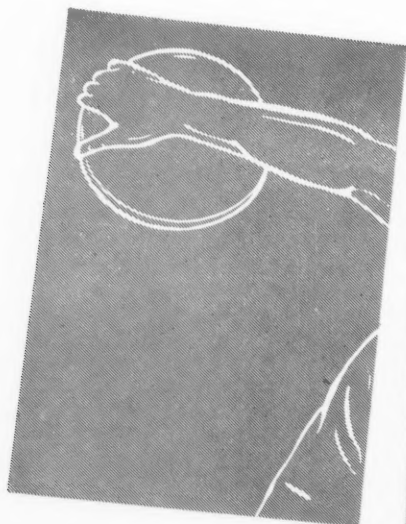
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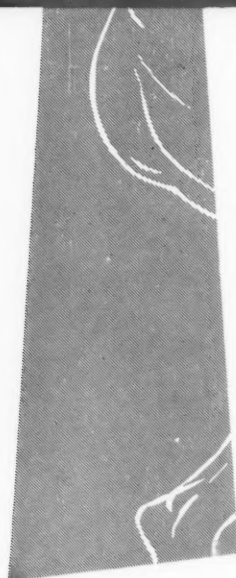
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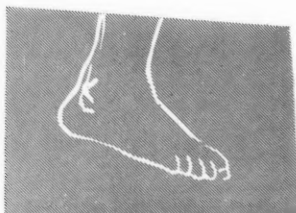
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FORTY YEARS OF NEPHROSIS IN CHILDHOOD*

BY

DAVID LAWSON, ALAN MONCRIEFF and WILFRID W. PAYNE

From The Hospital for Sick Children, Great Ormond Street, and the Institute of Child Health, London

(RECEIVED FOR PUBLICATION JUNE 19, 1959)

This article is an attempt to relate the present-day outlook on nephrosis in childhood with the 'natural history' of the disorder as it was seen at The Hospital for Sick Children, Great Ormond Street, in the days before modern treatment was available. The first period of the study is the responsibility of one of us (D.L.) and covers the years 1917-38. During the war years in-patient care of the children attending this hospital was widely dispersed and records are not always available. With the opening up of the hospital to more than a handful of patients in 1945 and the development of a new index system the study starts again and covers up to 1956-7. This period falls into two parts: for 1945-51 it had become possible to prevent and treat infection in children with nephrosis by means of sulphonamides and antibiotics; from 1951 steroids became available, at first in limited supply for selected cases, and in 1955 freely available for all cases as required.

The Hospital for Sick Children, Great Ormond Street has a large turn-over of patients and serves a wide area. This means that large numbers of case records have to be read and details checked before a child can be accepted as qualifying for inclusion in the series. It also means that follow-up of children, especially after they have passed the age for attendance at the hospital, presents many difficulties.

Definitions

For the purpose of this study the term nephrosis is applied to a syndrome presenting four essential characteristics, namely oedema, gross proteinuria, lowered plasma albumin and raised blood cholesterol.

The disorder presents, usually in the absence of any constitutional disturbance or other symptomatology, with the unheralded onset of generalized oedema. In severe cases the child becomes universally waterlogged in the course of a few days,

although a slower but steady increase in oedema over the course of two or three weeks is commoner. The urine, which has usually been unremarkable in quality, although often moderately diminished in quantity, is found to contain from 500 to 2,000 mg. % of protein but only a moderately increased red cell content. Addis counts of up to 10 million are not uncommon but the haematuria seldom amounts to more than this and is almost never macroscopic. The serum cholesterol is usually raised at the 'onset' but, if not, it steadily rises in the course of a few weeks to levels between 400 and 2,000 mg. %. The plasma albumin concentration is always markedly decreased and may be below 1%.

An infection often precedes the clinical onset but it is seldom clearly streptococcal and is more often in the nature of a common cold or bronchitis. Subsequently, it is often found that such infections will precipitate a return of, or an increase in the degree of, oedema and it is easy to understand that such an episode may first bring the hitherto sub-clinical disorder to light. The oedema may last for a few weeks only or may persist over months or years with alternating remission and relapse. When onset or relapse can be closely studied biochemically, it is found that the oedema is the last of the signs to appear in relapse and the first to disappear in remission, with the possible exception of proteinuria. After such a variable course all the manifestations may clear and the disorder may appear to be healed. Death may occur in periods of severe oedema from biochemical and water-balance disturbances or from overwhelming bacterial infection to which these children are particularly subject; or there may be a gradual or rapid superimposition, at any phase, of the features of generalized renal failure and hypertension with final death in uraemia. The transient occurrence of nitrogen retention or hypertension, particularly common in periods of increasing oedema, does not however itself presage such a termination.

In the 1945-57 series clinical notes and biochemical

* A summary of this paper was given at the IX International Paediatric Congress, Montreal, in July, 1959.

records have been fairly complete; most of the cases could be followed up and re-examined and all were within the memory of authors or colleagues.

The extraction and definition of the 1917-38 series was more difficult because (1) records, and in particular biochemical investigations, were less complete; (2) there were no existing follow-up studies as out-patient records for the period did not survive the Second World War; and (3) the unity of this disease was not recognized at the time and cases were found under a wide range of diagnostic headings. Biochemical criteria were applied wherever possible, but in many cases a subjective element had to be introduced.

When the question of differentiation between nephrosis and acute glomerulo-nephritis arose, main reliance was placed on the following contrasting features in the natural history of acute glomerulo-nephritis: (1) sudden onset with urinary signs, often within 10-14 days of a streptococcal infection; (2) transient nature of the oedema; (3) rapid rise and fall in any transient initial nitrogen retention and hypertension; and (4) normal blood cholesterol and plasma protein at clinical onset.

Classification

For the purpose of analysis the cases have been placed in one of the four following groups:

Inactive. This means the absence of the four essential criteria already quoted. Albuminuria must not exceed 50 mg. per 100 ml. The electrophoretic pattern of the plasma proteins is normal.

Latent. There is no oedema but albuminuria is above 50 mg. per 100 ml. and blood urea and cholesterol levels may or may not be normal.

Active. This group consists of cases with the complete, potentially reversible nephrotic syndrome just described, who may have transient increases in their blood urea and blood pressure, and also cases who have progressed to the irreversible uraemic stage, as judged by a persistently high and increasing blood urea and an increasing blood pressure.

Dead. The cause may not always be directly related to the nephrosis.

The second group is the most controversial and must be further discussed. By oedema in a follow-up series is meant essentially the pre-tibial oedema of the child, otherwise apparently well, who is attending the out-patient department, not the water-logged condition of the in-patient which fluctuates so much and not always for obvious reasons. There is no simple way of screening patients other than by looking for the pre-tibial oedema. All such cases will have some degree of albuminuria. When the oedema goes the child is clinically normal, but there

may or may not be albuminuria of over 50 mg. per 100 ml. If there is no such albuminuria then the child will almost certainly come into the inactive group provided that the blood chemistry is normal. Strictly speaking therefore inactive means clinically normal (i.e. no oedema) and chemically normal. The latent group seems to contain three subdivisions: (a) clinically normal but still albuminuria of over 50 mg. per 100 ml.; (b) clinically normal but both albuminuria and abnormal chemistry; and (c) clinically normal, no albuminuria but blood chemistry not quite normal. It is recognized that this latent stage may persist, but it only appears in a very small number of the patients whose records have been analysed in the 1945-57 series and the transfer of such patients to either the inactive or active groups will not affect the main conclusions.

Description of Search (1917-38 Series)

The in-patient case records for this period are bound in volumes at the end of which is a diagnostic index prepared by the registrar. All these indices were searched and every case history examined in which there appeared the remotest possibility that it might be a case of nephrosis. These diagnostic terms included every case in which the word nephritis of any kind was used and any in which the words oedema or toxic oedema were used. This resulted in a close study of the records of 1,500 cases. The greatest care was taken to make this selection as accurate as possible, but in certain cases recourse had to be made to something closer to intuition than to scientific study in view of the paucity of records. The author (D.L.) who carried out this part of the work is however satisfied that the diagnosis was almost certainly correct in every case included and any doubtful ones were discarded.

Analysis. The total number of cases found in this way was 78. Of these 18 had died during the first or subsequent admission and 60 had been discharged and lost from the records (Table 1).

TABLE 1
SEARCH AND FOLLOW-UP (1917-38 SERIES)

In-patients' Records Searched	1,500
Accepted as nephrosis	78
Died in hospital	18
Follow-up attempted 1953	60
Follow-up failed 1953	44
Followed up 1953	16

An attempt was made in 1953 to trace these 60 cases. Letters were sent to them at the recorded addresses and if no reply was received a further letter was sent. In a number of cases the patients could be traced at these addresses and in others

information was given by the present occupier which led to their successful tracing subsequently. This search was completely unsuccessful in 44 of the 60 cases. Sixteen were successfully traced and of these five had died (Table 2).

TABLE 2
ANALYSIS OF 16 CASES SUCCESSFULLY FOLLOWED UP IN 1953 (1917-38 SERIES)

Died	5
Alive and well .. .	11
Active	0
Latent	1
Inactive	8
Unclassified .. .	2 (in perfect health but not examined)

The remaining 11 were asked to come to the out-patient department for clinical and biochemical examination and nine did so. None of these had had any clinical relapse since his admission to hospital in childhood. All were in perfect health and none showed any clinical or biochemical evidence of activity or of sequelae of any kind, except for one woman who had borne children without mishap but whose urine contained 100 mg.% of protein. This technically places her in the latent rather than the inactive group. The remaining two were unable to come but sufficient information could be obtained to ensure that they were in perfect health.

Causes of Death (1917-38 Series). The 23 known deaths in this series have been classified as follows (see Table 3):

TABLE 3
ANALYSIS OF CAUSES OF DEATH (1917-38 SERIES)

	No. of Cases
Bacterial infection .. .	9 (includes 1 measles)
Treatment	5
Uraemia	4
Water and electrolyte disturbance (includes D. and V.)	3
Diphtheria	1
Unknown	1
Total	23

(1) INFECTION (nine cases). In all cases this was a bacterial infection with the exception of one child who died in a severe attack of measles. In the majority of cases the infection took the form of cellulitis, peritonitis and pneumonia, often accompanied by a septicaemia. There have been excluded from this heading infections which were the direct result of treatment.

(2) DISTURBANCES OF WATER AND ELECTROLYTE BALANCE (three cases). This includes children who died from overwhelming oedema and also those in

whom the cause of death was given as 'gastro-enteritis'.

(3) URAEMIA (four cases). Children who died in chronic uraemia with or without hypertension.

(4) DEATH DUE TO TREATMENT (five cases). This includes two children who died suddenly following over-rapid paracentesis, one who died of post-operative pneumonia following a renal biopsy, one who died with convulsions without previous nitrogen retention in the post-operative period following a decapsulation operation, and one who died following decapsulation, paracentesis and subsequent wound infection.

(5) UNCLASSIFIED (two cases). One appears to have been in perfect health for some years following discharge but died of diphtheria, and one died after discharge but the cause of death is unknown.

Of 21 cases in which the cause of death is known, therefore, all but four are deaths which could probably have been avoided had modern techniques of fluid and electrolyte balance and modern chemotherapeutic agents been available, and if methods now known to be useless and dangerous had not been used.

Estimate of Mortality (1917-38 Series). Of the total of 78 cases 18, or 23%, died during an initial or subsequent admission to The Hospital for Sick Children. In view of the incompleteness of the follow-up it is not possible to make a very accurate assessment of the subsequent mortality of the cases who were discharged alive. The first question to be answered is whether or not it is reasonable to assume that the 16 cases who could be traced were a representative sample of the 60 in which the attempt was made. This turns on the question of whether it is likely to be more difficult to trace patients who have died than to trace those who have survived.

TABLE 4
ROUGH ESTIMATE OF MORTALITY (1917-38 SERIES)

No. in series	78
Death in hospital .. .	18
Deaths after discharge 5 out of 16, equivalent to 19 out of 60 .. .	19
	37
Mortality approximately 37 out of 78=47%	

It is in fact the families rather than the individual patients who are being traced, and there seems no reason to think that it would be more difficult to trace the family of a child who had died than of one who had survived, although it is possible that the families of children who have died might be less willing to reply if they received the letter. Of the 44 untraceable cases, in all but four the follow-up letters were returned by the Post Office marked 'Not known at this address'. There were only four cases

in which letters were not so returned by the Post Office and had therefore presumably been accepted at the address given. In these circumstances it is considered reasonable to assume that the 16 cases traced may be regarded as a representative sample of the 60 and the approximate overall mortality of the series is as follows: Five of the 16 are dead; therefore of the total of 60 it may be assumed that 19 are dead. To these 19 presumed dead must be added the 18 who are known to have died while in hospital, giving an overall mortality of 37/78 or approximately 47% (Table 4).

It therefore appears that in the years 1917-38, before the days of antibiotics and steroids, the recovery rate was of the order of 50% and that of 21 cases in which the cause of death is known all but four (or approximately 20%) were due to causes which might have been averted by modern methods of control of infection and water balance disturbance.

Description of Search and Analysis (1945-57 Series)

For this period of the study indexed diagnoses and a special list held by one of us (W.W.P.) were accepted in the first instance, and during the 12 years or so covered the number of children classified as nephrosis was 123. Of these, five were private patients under the care of colleagues, and for various reasons records were not always complete nor was follow-up easy to arrange. They have therefore been omitted. Some of the remainder were seen as out-patients and transferred to other hospitals at once or after a short period. Their records have been used only in regard to age of onset and ultimate fate, if known. One of us (A.M.) read all the case records and reduced the data to a single *pro forma* sheet. This proved a fascinating but formidable task. Patients were often in hospital for long periods or were admitted on several occasions. (The record was held by one child admitted 23 times.) When no recent information existed this was obtained by seeing the child, by writing to the family doctor, to another hospital and so forth. As already mentioned, patients come to the hospital from a wide area and the tracing of them after discharge has been extremely difficult.* Altogether

* It may be mentioned in passing that successes in tracing included details obtained and contacts re-established in numerous ways. The police traced the address of one family; another patient was found after an announcement of her marriage engagement in *The Times*; the trail of one began in Wales, followed to a wrong part of East Africa, eventually finished in Central Africa and the child was seen in Out-patients when the father was next on leave. (She had actually made an apparently complete recovery which early records would not have suggested.) The Service authorities have been most helpful in tracing patients overseas, one going as far as Singapore. In other areas the health authorities have been most helpful and family doctors most willing to assist. One child in Malta, who was an in-patient, has been reported on whenever necessary.

failure has to be recorded for four children in the 1945-57 series. One is the child of a United States Air Force officer who has returned to the U.S.A. and, despite every possible effort on the part of the authorities, the present whereabouts are unknown. Three others were all going downhill shortly after the end of the war and cannot now be traced. Two of these were in fact rejected on further study of the records and are included in the 12 rejects to be mentioned later. Therefore of the true nephrotics in the series only two have been lost. After deducting lost patients, exclusions and transfers, there are 102 left for the purpose of estimating gross results and other factors (Table 5).

TABLE 5
PERIOD 1945-57

Case records abstracted	123
Selected in error	1
					<hr/> 122
Private patients	5
					<hr/> 117
Excluded on further scrutiny	12 (2 not traced)
					<hr/> 105
Transfer and no follow-up	1
					<hr/> 104
Not traced	2
					<hr/> 102

As already pointed out, this period can be divided into two main sections. Up to 1951 chemotherapy was available and then steroids were introduced, at first (since the supply was short) for limited and selected cases and by 1955 for all considered suitable. Detailed analysis as regards treatment will be given later. Here the gross results are considered according to the definitions already set out. In the 102 children successfully followed the disorder is considered to be inactive in 49, latent in nine and active in six. The remaining 38 are dead. This gives a crude recovery rate of about 50% or the same as in the 1917-38 series when neither chemotherapy nor steroids were available. There is however a strong suggestion, supported by a small number of cases, that maintenance methods of using steroids have remarkably altered the picture.

A histogram (Fig. 1) illustrates the distribution on the basis of age at onset of the oedema, showing the usually accepted peak between 1 and 5 years of age. The deaths are very much the same proportionately for each age group throughout the series. The three children with a recorded onset before 6 months of age are the subject of a special note on congenital nephrosis on page 125.

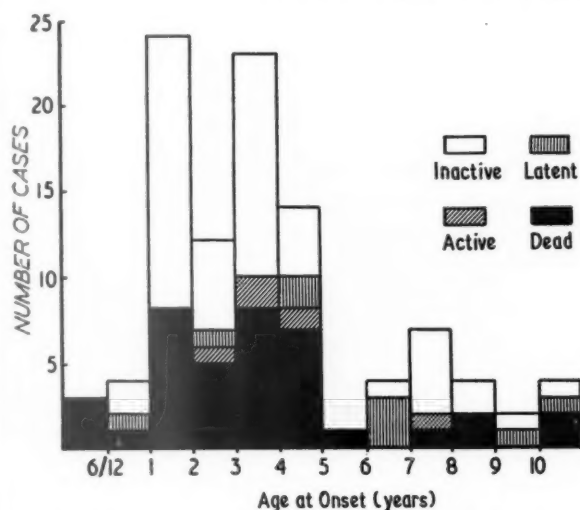


FIG. 1.—Histogram showing age at onset in 102 cases of nephrosis (1946-57 series).

The totals for the whole series are shown in Table 6. This shows a higher incidence in boys and a slightly higher mortality rate among boys than

TABLE 6
GROSS RESULTS (1945-57 SERIES)

	Total	Boys	Girls
Cases followed	102	59	43
Inactive	49	25	24
Latent	9	6	3
Active	6	5	1
Dead	38	23	15

girls. The numbers for latent or active cases are, as already mentioned, small in relation to the clear-cut groups of a satisfactory or fatal ending.

Table 7 gives details of the records of 12 patients in the 1945-57 series which, on final scrutiny, have not been included in the total of examples of nephrosis. Reasons for the rejection are given in the final column. The other columns indicate why at first sight the records appeared to justify inclusion. Since over half are known to be dead, and most of the others to be going down-hill, it seemed important to remove them from the series, otherwise they would have erroneously weighted the dead, active or latent groups.

TABLE 7
NEPHROSIS RECORDS REJECTED ON FINAL SCRUTINY (1945-57)

Name	When First Seen					Reasons for Rejection
	Age (yr.)	Oedema	Urinary Proteins (mg. %)	Total Serum Proteins (mg. %)	Blood Cholesterol (mg. %)	
Kenneth B. ..	12	Nil	440	4.7	Not done	No oedema; persistent haematuria; probably chr. nephritis
Margaret D. ..	2½	+++	1,500	3.6	870	Raised blood urea; haematuria type 2 nephritis from onset; acute nephritis 8 mth. before
Raymond E. ..	7½	+++	700	3.3	470	Haematuria ++; scarlet fever 3 yr. before; chronic nephritis
Daniel H. ..	8	Minimal	700	5.62	208	Hypertension; hepato-splenomegaly; chronic nephritis
Peter H. ..	10	++	Nil	3.02	367	Never any albuminuria at G.O.S.; ? 'cured' before admission; oedema for 7 weeks at age 4½ yr.; lost to follow-up
Michael H. ..	3½	+	140	4.49	386	Latent stage when first seen; died chronic nephritis age 10 yr.
Michael K. ..	1½	+++	Gross	3.62	394	Transferred
Peter L. ..	1	Nil	800	4.6	356	No oedema at any time; persistent red cells in urine
Vera M. ..	9	Slight	800	4.4	—	Lost in follow-up; raised blood pressure; acute nephritis aged 9 yr.
Lohan M. ..	9	Nil	1,000	5.6	—	No oedema; blood urea 148 mg. %; died chronic nephritis
Christopher S.	4	Nil	375	5.9	166	No oedema at first attendance; latent in 1951
Juan S. ..	6½	Slight	400	5.3	206	Fibrocystic disease; cirrhosis of liver; died aged 7½ yr.

Results of Treatment (1945-57 Series)

In the 1945-57 period a low salt and high protein diet was almost universally the basic treatment for cases of nephrosis while in hospital. Sometimes a diet which was almost salt-free was given, but sometimes it was found to produce abnormally low levels of serum sodium while oedema still persisted, and it is now rarely used. As well as this basic diet, various other forms of treatment were tried.

Thyroid. It was for a long time considered that thyroid had a place in the treatment of nephrosis and many cases were given this substance. Some cases were given thyroid up to the level of tolerance, shown usually by the onset of diarrhoea. In others normal therapeutic doses only were given ($\frac{1}{4}$ -1 gr. thyroid daily).

Resins. With the introduction of resins, in a form suitable for therapeutic use, a group of children was treated using various types of resin. The results have been published in more detail elsewhere (Payne and Wilkinson, 1951).

Diuretics. Several types of diuretic have been used.

UREA. When urea is used as a diuretic it has been found necessary to give relatively large doses, such as 15 g. a day, and at the same time to restrict the fluid intake. Until the blood urea reaches approximately 100 mg.%, diuresis does not occur. When this level is reached diuresis follows in some cases. In others, unfortunately, no diuresis occurs. Increasing the blood urea to a higher level almost invariably produces such severe discomfort that it is impractical as a form of treatment. The misery of the child in these circumstances is most striking. When successful, the treatment can be maintained for many months.

WATER. Diuresis will result from forced water intake. Again this is by no means always possible. In some cases there is an initial retention of water and then any excess water given is excreted quantitatively. In other cases the excess water carries with it some of the oedema and a genuine diuresis occurs with loss of oedema.

MERCURIAL DIURETICS. Mersalyl was the most frequently used and, as with other diuretics, there was sometimes an initial diuresis which in general was not maintained with further doses.

NON-MERCURIAL DIURETICS. Usually these have had no effect but occasional diuresis has occurred with the first few doses. Subsequent doses have proved ineffective.

Fever. In a few cases production of fever, either by measles or malaria, has been used, but the

numbers are too small for use in this study. Usually there has been an initial loss of oedema followed in almost all cases by a return of oedema at varying intervals of time.

In Table 8 the results of individual treatments are shown, the results being classified as inactive, latent or active, according to the child's condition at the end of any particular period of treatment. The majority were on a basic low-salt high-protein diet and antibiotic treatment when necessary. Examination of this Table will, of course, show many more case treatments than the actual number of children. It will be seen that the number of cases classified as inactive occur mainly in the group which had rather prolonged treatment on the basic diet alone.

In two of the 36 treatments with urea the inactive state was reached, but the other diuretics, resin or water, produced only a transient improvement: five of 14 cases treated with water and 10 of 36 cases treated with urea became latent. Of the 23 cases receiving the basic treatment plus thyroid, five became inactive and six latent, and of the 49 case treatments in which no specific treatment other than the basic diet was given, 16 became inactive and 13 latent.

TABLE 8
RESULTS OF TREATMENT (1945-57 SERIES)

Treatment	Number	Result		
		Active	Latent	Inactive
Basic alone	49	20	13	16
" + thyroid	23	12	6	5
" + resins	13	12	1	0
" + urea	36	24	10	2
" + water	14	9	5	0
" + other diuretics ..	19	18	1	0
None	—	—	—	10

It will thus be seen that no better results were obtained when any specific treatment was given than when basic treatment alone was given. In fact, since the duration of the basic treatment was normally much longer than that of the specific treatment, the results appear much better.

The total number of cases not receiving steroids and becoming inactive in this group was 33: 10 recovered after being discharged and were presumably on no particular treatment at all.

Steroids. These became available in small amounts in 1951. A few cases were treated in the first years, and subsequently the use of steroids as the main treatment became general. Since 1951 the way in which steroids have been used has changed considerably and, largely owing to the more critical examination of results, the general aim of individual treatment has altered. Before steroid treatment

there was no known method whereby the albuminuria could be controlled, and most clinicians planned the treatment of their cases on the basis of getting rid of the oedema and hoped that the albuminuria and other abnormalities would clear up in time, but the disappearance of the oedema was regarded as the therapeutic aim. (This point is discussed at greater length later.) It was on the disappearance and re-appearance of oedema that the reputation for frequency of spontaneous remissions and relapses in nephrosis was based. If the stricter criteria for apparent recovery are used, it will be seen that, although there is still a liability to relapse, it is by no means as frequent as was previously considered.

The records have been examined using these stricter criteria and, of the 15 children who reached the inactive phase and had had steroid treatment, two cases only relapsed, one recovered spontaneously and the other recovered after further treatment. In 22 cases of children not receiving steroids, who reached the inactive stage, only one case relapsed, and that case also made a spontaneous recovery. However, in the steroid-treated cases who have reached the inactive stage relatively recently, intercurrent infections may cause a transient return of the albuminuria, lasting from a few days to two or three weeks and disappearing without treatment.

Initially, short courses of steroids were given, either ACTH or cortisone. ACTH was usually given for eight to 10 days in varying doses, usually 20 to 40 mg. daily, and cortisone in doses from 100 to 200 mg. daily for approximately 10 days. In both cases at the end of that period treatment was abruptly stopped. This was called the short treatment. In most cases diuresis occurred and generally oedema disappeared but albuminuria, although frequently lessened, was generally still present and in most cases the oedema returned later on.

The next phase was to give larger doses, 200 to 300 mg. of cortisone, or the equivalent of prednisolone, or if ACTH was used, 80 mg. daily using the gel in divided doses. This treatment was maintained for approximately one month and then the steroids were tailed off fairly quickly, usually within two to three weeks. This type of treatment has been called long-term. In general in these cases the albuminuria disappeared only to reappear as the dose was being tailed off or very shortly afterwards.

In the next form of treatment, called maintenance treatment, steroid therapy has been maintained at a slowly decreasing level for much longer periods. There is much difference of opinion as to the ideal way of doing this. In the majority of the maintenance cases an initial month's treatment is given

similar to that in the long-term, by which time there is usually no albuminuria and the plasma proteins are approaching normal while the cholesterol is falling. The dose is then cautiously reduced by 10 to 15% every week at first and later every fortnight. This slow reduction is continued as long as there is no albuminuria. Usually within two to three months the plasma proteins are chemically and electrophoretically normal and the cholesterol also has returned to a normal level. If these values are slow in returning to normal the therapy is continued for a longer period and the intervals between reductions are increased. If albuminuria returns during the period of reduction, the dose of steroid is increased until it disappears again. Reduction is then carried out more slowly.

In a few cases the intermittent high dosage treatment was used, 400 mg. cortisone three days in succession, followed by four days without steroid.

In assessing the final outcome, the cases have been divided into two groups, those who have received steroids and those who have not. The results are given in Table 9. The results in this Table are

TABLE 9
RESULTS OF TREATMENT WITH STEROIDS

	No Steroids		Steroids	
	(no)	(%)	(no)	(%)
Total cases	62		40	
Inactive	33	53	16	40
Latent	5	8	4	10
Active	4	7	2	5
Dead	20	32	18	45

somewhat unexpected. It appears that the results from steroid treatment are definitely inferior to those when no steroids are given. One possible explanation for this is the inclusion in the steroid group of cases carried over from the previous group which were already doomed to failure.

Table 10 is an analysis of the deaths in the two groups. Uraemia accounted for more than half the deaths but, whereas 10 cases of uraemic death

TABLE 10
CAUSES OF DEATH

	1917-1938	1945-1957	
		No Steroids	Steroids
Uraemia	4	10	10
Heart failure	—	1	2
Infections	10	3	2
Cystinosis	—	2	—
Pulmonary embolism	—	—	2
Electrolyte imbalance	3	—	—
Treatment	5	2	2
Not known	1	2	—
Total	23	20	18

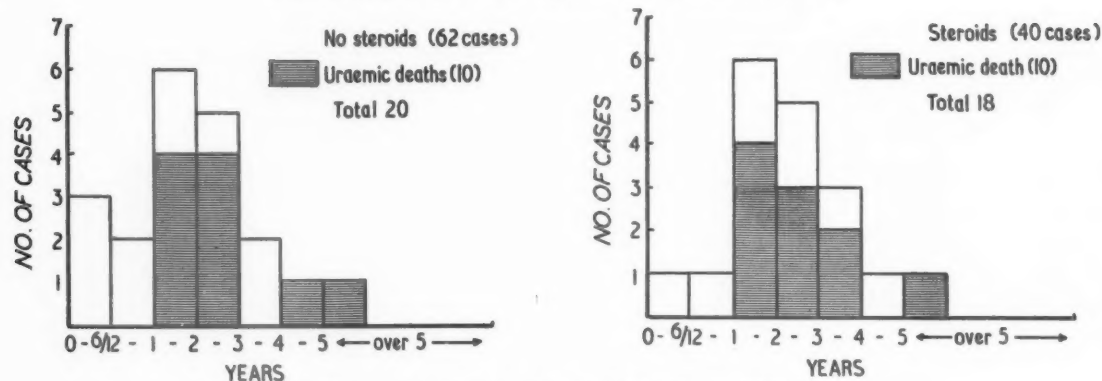


FIG. 2.—Histogram showing duration to death in 38 cases (1945-57 series).

occurred out of 62 non-steroid cases, the same number occurred in only 40 cases given steroids (Fig. 2). Although this suggests a slight increase in uraemic death, it is hardly sufficient to account for the difference in the two groups. A more detailed analysis of the effects of steroid treatment based on individual treatments using the same criteria as in Table 8 is shown in Table 11. In this Table are included cases treated in 1957-58 which were not included in the 102 cases under survey. This Table brings out the difference in ultimate results between the short, long and maintenance types of treatment, and largely explains the apparent inactivity of steroids shown in Table 9.

TABLE 11
RESULTS OF TREATMENT WITH STEROIDS

	1951-57			1957-58			
	Short	Long	Maintenance	Short	Long	Maintenance	No Treatment
Total treatments	35	36	6	3	8	4	1
Inactive	0	10	6	0	2	4	1
Latent	10	13	0	0	0	0	
Active	25	13	0	3	6	0	
'Cure' %	0	28	100	0	25	100	

The numbers treated on maintenance are not significant and the 100% cure reached is certainly accidental and is partly due to the fact that only cases whose treatment had been completed were included in this Table. In order to appreciate more fully the effect of steroid treatment a study of Table 8 (individual treatments, non-steroid) is necessary. It is apparent from this that no individual treatment produces as good results as simple dietary measures alone, or even no treatment at all. It is against this background of spontaneous remission that the results of steroid treatment should be assessed.

In Table 12A the length of time elapsed between onset of disease and cure, in the steroid and non-steroid cases, is compared, and it will be seen that steroid treatment definitely produces more rapid cure.

In Table 12B the time relationship between onset and death shows that in the fatal cases there is no material difference.

Tables 12C and D show the ultimate result and the interval of time between onset of disease and the start of steroid therapy. There is no suggestion in these Tables that better results are obtained when steroid therapy is started early.

TABLE 12

A	Time between Onset and Cure					Total
	<6 mth.	6-12 mth.	1-2 yr.	2-5 yr.	>5 yr.	
No steroid	(no.) 5	(no.) 4	(no.) 4	(no.) 13	(no.) 7	33
Steroid	2	2	3	9	—	16

B	Time between Onset and Death					Total
	<6 mth.	6-12 mth.	1-2 yr.	2-5 yr.	>5 yr.	
No steroid	3	2	6	8	1	20
Steroid	1	1	6	9	1	18

C	Time from Start of Steroid Therapy to Cure					Total
	<6 mth.	6-12 mth.	1-2 yr.	2-5 yr.	>5 yr.	
	7	1	2	6		16

D	Interval between Onset of Disease and Steroid Therapy					Total
	<6 mth.	6-12 mth.	1-2 yr.	2-5 yr.	>5 yr.	
Cure	8	2	3	3		16
Death	9	3	4	2		18
Latent or active	2	1	1	2		6

In analysing the causes of death the hazards of treatment have to be considered. In the period 1917-38 it will be observed that a fair number of deaths can be attributed directly to treatment. It is not quite so obvious in the period 1945-57 but a suspicion by one of us (A.M.) that mersalyl was a dangerous treatment has been confirmed. The results in 12 cases treated with mersalyl are: inactive (1), latent (1), dead (10). These results strongly suggest that mersalyl in itself is dangerous. That it was used merely as a last resort was not found to be the case on examining the notes, since in most cases it was given in the first 12 months from the onset of disease.

It must be realized that steroid treatment is potentially dangerous and the group of cases we have treated shows the following results:

Died of overwhelming infection	1
Sudden cardiac failure and death on the fourth day of cortisone treatment	1
Decalcification of vertebrae	1
Acute cerebral crisis with unconsciousness and fits (? cerebral oedema), with ultimate recovery	1
Adrenal crisis, low blood pressure, low serum sodium and collapse	2

Thus, of the 18 steroid deaths, two can be attributed to steroid therapy, and both the cases of adrenal crisis could quite well have been fatal if they had not fortunately occurred while in hospital.

Discussion

The literature on nephrosis threatens to become unmanageable. This paper is essentially concerned with a presentation of facts as ascertained from a study of the disorder in childhood in hospital records for over 40 years. It is not proposed to discuss the pathology or pathogenesis. The definitions already set out indicate what sort of disease process is being considered. The results of treatment, with special reference to those obtained by the use of steroids, can usefully be compared with those presented by McCrory and Fleisher (1958), Metcoff (1958) and Riley and Scaglioni (1959). A useful historical survey was given by Mann (1958) on the occasion of the Bright centenary celebrations.

If the assumptions made in the section which considers the 1917-38 series are accepted as correct, then about half the patients are dead. In the 1945-57 series as a whole about half are either dead or in an active or latent phase. Some of those classified in the last two categories at the time of assessment may by now have moved or will move into the inactive group, so that broadly speaking these results probably show a slight improvement over the results of 1917-38, but certainly not as great an

improvement as might have been expected with the better control of infection and, in the later cases, an active agent to attack what is probably the fundamental lesion which leads to the proteinuria. Again, if the 1945-57 group is broken down into those who did not receive steroids and those who did, there is no dramatic improvement with the new drugs, at any rate in the early years before the best method of using steroids was worked out. Indeed, taking the overall figures as shown in Table 9, there is a 45% mortality rate in the steroid-treated cases compared with only 32% in those not receiving steroids, with 15% in each group still classified as latent or active.

A review of the causes of death in each of the three periods shows that 17% died of uraemia in the pre-antibiotic era, the remainder dying from causes such as infections, which now would be regarded as curable. Since the introduction of antibiotics the cause of death has changed and is now uraemia in over 50% of cases (Table 10).

However, deaths which would have been theoretically preventable still occur and in the final analysis uraemia and heart failure seem to be the expected causes of death in nephrotic children. A small unknown proportion of these uraemic deaths will be due to unavoidable errors in initial diagnosis, such as in those cases shown in Table 7, which were retrospectively rediagnosed. Until more certain means of diagnosis are utilized (such as renal biopsy), this error will prevent an accurate prognosis, and therefore a proper evaluation of treatment, being made. From studies already published (Vernier, Farquhar, Brunson and Good, 1958) it is likely that in the majority of cases the correct diagnosis can be made in the early stages of the disease. Thus, a death rate from uraemia and heart failure of 23% of all recent cases (and it will become higher, since many of the still active cases are already uraemic) indicates that a proportion of 'pure nephrotic' children will die of uraemia. A small proportion will still die of intercurrent accidents, preventable or not; the remainder, if they can be kept alive, should recover. It is impossible to assess this figure accurately, but it is over 50% and probably about 60-70%, as judged by the non-uraemic causes of death. Any treatment must have a 'cure' rate of about 80-90% before it can be regarded as of real value. Table 12 shows that the majority of deaths occur within the first five years of the disease, so it should be possible to determine if a given treatment has successfully prevented the development of uraemia when enough cases have been treated for over five years. At the present moment the evidence is only sufficient to indicate a promising trend.

In considering the value of many of the remedies used, the aim of the treatment at the time must be borne in mind. Until quite recently the physician's primary aim was the cure of the oedema, with the hope that in due course the remaining pathological changes would cure themselves. With such an imperfect criterion of cure it is not surprising that relapses were many and frequent. Thus, when examining Table 8, all the latent results would have been called cures. Even with this proviso, it will be seen that the more common methods of therapy were quite ineffective when compared with the basic treatment (low-salt, raised-protein diet). In a small series of eight cases treated with measles and two with malaria, seven reached the latent stage, but only one became inactive without further relapses.

Since the oedema most frequently causes the patient to consult a doctor, its disappearance must have a good effect on the outlook of the child and his parents, although there is no direct evidence that removing oedema improves the prognosis. Thus it is reasonable to take non-specific measures which will help in its removal, providing that they are harmless. For example, urea, resins, water and occasionally non-mercurial diuretics are useful. For the same reason a low-salt diet is given.

Oedema, if severe, can be very distressing and can even endanger life. In these cases acupuncture of the dependant legs and abdominal paracentesis, both under antibiotic cover, have been used and occasionally a complete remission has followed.

Steroid treatment has undoubtedly made a big change in the method of treating nephrosis. In the early days, when removal of oedema was the therapeutic aim, short eight to 10 day treatments were used with an initial gratifying effect but, as with previous methods, relapses occurred, which were more resistant to further treatment with steroids. The aim of treatment was altered to complete reversal of all pathological changes. Much longer terms of treatment were used and the results began to be more encouraging. While, as yet, no uniform method has been arrived at, the general principle is to give adequate dosage of a steroid preparation, the equivalent of 240 to 300 mg. cortisone daily. It does not appear to make much difference which of the new, less sodium-retaining steroids is used. Treatment is continued for six to 12 months according to the plan for reduction already mentioned. Clinically it seems that it needs many months to reverse completely the pathological changes in the glomerular basement membrane, if indeed this can be done. Since it is probable that some 20-30% of untreated patients will progress to irreversible renal damage, the

essential fact to determine is whether in these cases it is possible to prevent this.

As has been pointed out, this can only be done when sufficient time has elapsed for such changes to develop—at least five years. This delay in making a judgment of cure is necessary since steroid therapy can remove the nephrotic symptoms for a time in cases in which the diagnosis is known not to be simple nephrosis. Until an adequate period has elapsed it is possible only to say that the latest results are promising in that a high percentage are reaching the inactive stage.

It has frequently been stated that liability to a return of nephrosis can never be eliminated. It is clear that clinical relapse is common if only the latent stage is reached. When the inactive stage is reached relapse is less frequent but may still occur. Many patients, whose nephrosis has been successfully treated with steroids, for some years tend to get transient albuminuria during fairly mild intercurrent infections. In a few this proceeds to a full relapse which may need a further course of steroids.

This raises the fundamental question of the aetiology of nephrosis. Should the condition be regarded as an inborn liability of the kidney to a special type of pathological response to certain insults, or should the pathological response be regarded as due to a specific insult, such as is believed to occur in acute nephritis following infection with certain types of streptococci? If the former view is held, it is unlikely that any form of treatment will prevent recurrence of symptoms even many years later. In the second possibility, once a cure is complete, relapse would only occur with a further specific insult. Such clinical evidence as exists suggests the former view as being possibly the more likely since occasionally relapses have recurred after many years of freedom from symptoms.

To sum up, the natural course of nephrosis, if intercurrent infections are adequately dealt with, is for at least 50% and probably nearer 60-70% of the patients to be cured, but there is also an inborn liability to relapse. There is in every series, based on clinical diagnosis alone, a small group with a different pathological basis and a bad prognosis. No treatment has yet been shown to improve the ultimate prognosis, although some treatments have worsened it. The most recent method of steroid therapy, while very promising, has undoubted hazards which must be balanced against the present uncertainty that permanent improvement in prognosis will occur.

Since delaying the start of steroid therapy does not seem to affect the ultimate result (Table 12D) and since a proportion of untreated cases remit

spontaneously within a few months (Table 12A), delay of up to three months in starting steroid therapy is suggested to allow time to see if there are signs of spontaneous improvement. There is no evidence that any adjuvant treatment has a material effect, apart from the need to give an adequate protein diet and to keep the salt content low when there is oedema, especially during steroid therapy. Complete bed rest, except when there is gross oedema, is not necessary. A change from prolonged bed rest to reasonable activity at The Hospital for Sick Children caused no worsening of the prognosis and a decided improvement in the children's morale. Another advantage of permitting reasonable activity is that the child can be sent home and attend school when desired while still on steroid or other therapy.

It is difficult to assess the value of the routine use of antibiotics. Oral penicillin has been used in the present series ever since it became available, reinforced by other antibiotics if an intercurrent infection occurred. This has been quite successful, and it has not been necessary to reduce steroid dosage because of infection. Prophylactic antibiotics or sulphonamides have been used to try to prevent intercurrent infections, but they have not been successful.

Note on Congenital Nephrosis

Three of the children in the 1945-57 series manifested the nephrotic syndrome at or within a few weeks of birth and all died. Two of these were siblings (boy and girl) whose parents were first cousins and they have been reported elsewhere together with a third case (not in the Great Ormond Street series) whose parents were also cousins (Giles, 1957). Briefly, the post-mortem changes were mainly in the proximal tubules, and doubly refractile crystals were present. It is likely that the whole condition was related to cystinosis.

The third child in the present series was the first child of unrelated parents who have since had a normal child. Her eyes were reported as swollen at birth and there was a sudden weight gain about the tenth day. Generalized oedema appeared at about the fourth month. She was given mersalyl at another hospital and later referred here because of a persistent urinary tract infection. Her condition satisfied the four criteria for nephrosis and no improvement was achieved by the use of thyroid extract, blood transfusion, urea or decapsulation of the kidneys. The kidneys at operation were pale and soft with no scarring. No biopsy was done. A year later on re-admission she had no oedema but the blood pressure was raised to 140 mm. Hg, the blood urea was 340 mg. % and there was an albumin-

uria of 650 mg. % She died at home at the age of 2½ years. No autopsy was performed.

Another infant admitted to The Hospital for Sick Children in February, 1958, born after a normal pregnancy and delivery and weighing 5½ lb., developed generalized oedema on the third day of life. (He was the first child of the present marriage of unrelated parents; the mother had had two normal children by a former marriage.) The oedema subsided after two days and recurred at the age of four weeks, leading to admission under the care of a colleague (Dr. A. P. Norman). The infant satisfied the four criteria of nephrosis and electrophoresis showed a typical nephrotic pattern. Urinary amino-acid excretion was within normal range. He was treated with steroids and antibiotics. Very troublesome diarrhoea caused great difficulties in oral feeding and he died after a sudden collapse at the age of 3½ months. Autopsy (Dr. M. Bodian) showed bilateral renal vein thrombosis of long standing with some extension into the inferior vena cava. The changes in the kidneys were those associated with nephrosis.

These five cases illustrate various ways in which nephrosis may be caused very early in life. Poisoning by mercury is another possible factor. The position briefly is that congenital nephrosis or neonatal nephrosis is likely to be due to mechanisms other than those causing the more usual type of nephrosis such as is dealt with in the present report.

Summary and Conclusions

A study of nephrosis as seen at The Hospital for Sick Children during the last 40 years has been made. The cases have been divided into three groups: (1) pre-antibiotic 1917-38; (2) antibiotic, and (3) steroid. The recovery rate in the first group was approximately 50% and much of the mortality was due to infection. In those survivors followed-up in this group there was no instance of relapse after the final hospitalization period. The recovery rate in the second group was 53% and in the third 40%, and in these last two groups the mortality from uraemia was very much higher.

While the control of infection and of water balance has clearly improved the short-term prognosis, none of the other methods of treatment, including short-term steroid therapy, appears to have had any very striking effect on the mortality.

Before there was any method of treatment which strikingly affected the basic sign of proteinuria and its associated biochemical disturbances, attention was focused on the control of infection and on the treatment of oedema. Experience has shown that the treatment of oedema *per se* is not particularly

important except when the oedema is so severe as to be disabling in itself.

The observation that steroids could bring about a complete biochemical remission in the large proportion of cases has switched attention from protective and palliative treatment to the idea of curative treatment. With the advent of steroid therapy therefore the aim has become the complete reversal of all the pathological changes.

The results of various types of therapy have been compared. Until the technique of prolonged (six-12 months) steroid therapy was introduced, no specific therapy appears to have shown any advantage over simple basic dietary therapy and the control of infection with antibiotics.

Results in a small number of cases in whom long continued cortisone therapy has been given suggest, however, that permanent remissions may be obtained by this means, and raise the hope that the suppression of the biochemical disease in this way may reduce the incidence of that secondary nitrogen retention and hypertension which have become the major cause of mortality in recent years.

There is a high natural tendency to recovery. If all avoidable intercurrent incidents are excluded the natural remission rate is between 60 and 70%. In a reasonable proportion of cases of nephrosis spontaneous remission occurs within the first few months of the disease. As there is no evidence in this series that early treatment gives a better prognosis than that obtained when steroid treatment is delayed for some months from the onset of the disease, and since there are undoubted hazards from the use of steroids, it is suggested that steroid treatment of a new case should be delayed for a month or so to exclude the possibility of an early natural remission.

In our view the present aims of treatment should be as follows:

- (1) The control of infection with antibiotics

- (2) The maintenance of nutrition as far as possible with a moderately high protein intake
- (3) The partial control of oedema with a low-sodium (but not a sodium-free) diet
- (4) Long-term treatment with steroids in variable dosage sufficient to maintain urinary protein excretion at the lowest possible level.

By these methods it should be possible to maintain affected children in as good health as possible during the active phase of the disease, and to keep them out of hospital for most of the time, thus interfering with their lives as little as possible.

The success of long-term steroid therapy must be judged by the extent to which it reduces the incidence of renal failure, which has become the major cause of mortality.

Five fatal cases of congenital nephrosis are reported, with varying underlying pathologies.

Thanks are cordially expressed to colleagues on the staff of The Hospital for Sick Children, Great Ormond Street, for permission to include the records of their patients and in some instances to follow up the course of the disease; also to the Department of Medical Illustration for the histograms, and to secretarial staff for much patient typing and re-typing of drafts. The investigations recorded were undertaken under the auspices of the Research Committee of The Hospital for Sick Children.

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POISONING ACCIDENTS IN CHILDHOOD

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The problem of accidents in the home has recently received much publicity and the Government has called for special efforts in dealing with it. Attention is being directed mainly to traumatic causes such as falls, burns and scalds. Of the 900 deaths annually due to domestic accidents in children aged less than 15 years in England and Wales, the vast majority are due to these causes. During the past decade, however, between 16 and 47 (average 32) every year have been due to accidental poisoning and relatively little interest has been shown in this group. Until more is known of the epidemiology of these accidents the problem of prevention cannot be faced.

Paucity of information on the subject is probably due to several factors. The very wide selection of potentially poisonous substances taken by children makes generalization of their effects and sources very difficult. Many poisoning accidents produce no clinical effects (other than parental anxiety) and as a result are not investigated. The fatality rate is very low and does not reveal the extent of the problem.

It is difficult to estimate how many poisoning accidents there are in this country each year. Although there are many papers dealing with small or selected series (Holzel and James, 1951; Spencer, 1951; Craig, 1953) or describing single cases (Kirby, 1955; Hurdle and Lane, 1956; Greenberg, 1957) there is only one large series (Craig and Fraser, 1953) which refers to poisons in general. The fatality rate in this was two in 502 cases. The series described below includes one death in 275 cases. These two series combined show a fatality rate of 0.4% but times, places and possibly case selection differ. Several large series in the U.S.A. (Jacobziner, 1956; Mellins, Christian and Bundesen, 1956; Dobson, Daeschner, Mondshine, Teng, Preble and Knudsen, 1957; Jacobziner and Raybin, 1957; Schroeder, 1957) totaled 14 deaths in about 3,100 children, a fatality rate of 0.45%.

It seems likely, therefore, that for every death, about 250 children are admitted to hospital for observation or treatment of poisoning. This

suggests a total of 7,000 or more such accidents in this country each year. Poisoning thus plays a considerable part in childhood morbidity. Some of the factors in its aetiology are considered below.

Material

The case histories were examined of all children aged less than 16 years who were brought to Hillingdon Hospital because of poisoning or suspected poisoning between January, 1946 and March, 1958. The total number was 292. Seventeen were discarded as being irrelevant to this study of accidental poisoning by ingestion because they referred to coal gas poisoning (8), poisons deliberately taken or given (8) and poison absorbed from a raw skin surface (1). Of the remaining 275 children, 218 were admitted to the wards; the other 57 were treated in the casualty department. No child figured in more than one accident.

There were 156 boys and 119 girls. The average age of the boys was 2 years 10.8 months, that of the girls 2 years 8.2 months, and of the whole series 2 years 9.5 months. The age distribution is shown in Table 1. There was no appreciable difference in

TABLE 1
DISTRIBUTION OF POISONING CASES BY SEX AND AGE, JANUARY, 1946-MARCH, 1958

Age (yr.)	Male (no.)	Female (no.)	Total (no.)
0-1	5	4	9
1-1½	15	10	25
1½-2	37	31	68
2-2½	32	26	58
2½-3	19	14	33
3-4	21	14	35
4-5	11	10	21
5-10	13	10	23
10-16	3	0	3
Total	156	119	275

the age distribution between the sexes. The most susceptible age was between 1½ and 2½ years, this group including 46% of the total.

Incidence

The distribution of the children throughout the period is shown in Table 2.

TABLE 2
NUMBER OF CHILDREN ACCIDENTALLY POISONED,
1946-1957

Year	Number	Year	Number
1946	8	1952	21
1947	7	1953	28
1948	16	1954	25
1949	16	1955	46
1950	16	1956	39
1951	13	1957	32
		Jan.-Mar. 1958	8

The population which the hospital serves has increased only slightly during the period under review. Except at the periphery of the area there has been no alternative hospital for such cases. The annual numbers are therefore approximately comparable and show the great increase in accidental poisoning as noted in Edinburgh and Aberdeen by Craig and Fraser (1953) during the past decade. The peak incidence during this period was in 1955 (see Fig. 1). It is too early yet to determine what the trend over the next few years will be.

Seasonal variation in the incidence of accidental poisoning has been noted in the U.S.A. (Jacobziner, 1956) where 60% of cases occurred in the first half of the year. In the present series a marked variation occurred fairly consistently throughout the period. The pattern however was different. Only 40% occurred in the first six months of the year. More striking was the fact that 57% occurred during the five summer months of May to September (Table 3). This excess in the summer months was not due wholly to the ingestion of seeds, berries and plants, for, of 24 cases of this type of poisoning, 16 occurred in the summer and eight in the winter. It seemed partly related to the longer daylight hours (see below) though the greater wandering about the house which summer warmth permits may have been contributory.

TABLE 3
NUMBER OF POISONING CASES BY MONTH IN THREE-YEAR PERIODS, 1946-1957

Period	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
1946-48	2	1	3	2	1	5	2	7	4	0	1	1
1949-51	2	3	2	2	3	5	2	7	5	9	2	5
1952-54	1	4	3	4	13	9	8	9	9	7	3	4
1955-57	6	3	16	4	8	10	16	14	15	8	7	10
Total	11	11	24	12	25	29	28	37	33	24	13	20

Total for May-Sept. = 152
Total for Oct.-Apr. = 115

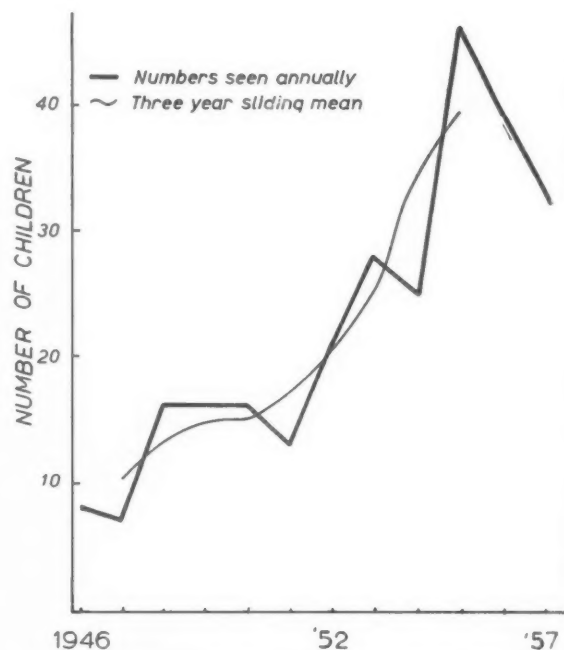


FIG. 1.—Annual numbers of children seen at Hillingdon Hospital because of accidental poisoning, 1946-57

Poisoning accidents occurred at nearly all hours of the day and night. Table 4 shows that the great majority (70%) occurred between 11 a.m. and 7 p.m. Separation of the accidents into summer and winter incidences indicated that there was an excess of accidents between 5 and 7 p.m. during the summer months (Fig. 2). It may be that this summer evening excess can be ascribed to the fact that small children are active for much longer hours in the summer and are likely therefore to be tired and less easily controlled in the evening.

Substances Swallowed

The substances swallowed by the children are listed in Table 5. The total of 285 is accounted for by the fact that one child took three substances and eight took two each.

TABLE 4

NUMBER OF POISONING ACCIDENTS BY HOUR OF DAY, SUMMER AND WINTER, AND HOURLY INCIDENCE, SUMMER AND WINTER (1946-1957)

Time	Number			Corrected Rate*		Time	Number			Corrected Rate*	
	Total	Summer	Winter	Summer	Winter		Total	Summer	Winter	Summer	Winter
midnight						noon	18	6	12	7.2	10.3
1-						1-	16	5	11	6.0	9.5
2-						2-	12	8	4	9.5	3.4
3-	2	1	1	1.2	0.9	3-	33	18	15	21.4	12.9
4-						4-	25	14	11	16.7	9.5
5-						5-	17	14	3	16.7	2.6
6-	1		1		0.9	6-	22	14	8	16.7	6.9
7-	6	4	2	4.8	1.7	7-	13	7	6	8.4	5.2
8-	13	7	6	8.3	5.2	8-	7	3	4	3.6	3.4
9-	8	6	2	7.2	1.7	9-	5	3	2	3.6	1.7
10-	12	4	8	4.8	6.9	10-	2	1	1	1.2	0.9
11-noon	21	11	10	13.1	8.6	11-midnight					

Number of accidents with time not recorded = 42

* Summer (May-Sept., 152 days) and winter (Oct.-Apr., 243 days) numbers have been corrected to represent an hourly incidence per half total period under review

The list is essentially similar to that of Craig and Fraser (1953), though the proportions of the groups of poisons differ slightly. Table 6 and Fig. 3 show the change in the incidence of the various groups throughout the period. Here several differences become apparent.

Within the medicament group several trends are apparent. The frequency of aspirin poisoning has been much enhanced since 1952 by baby type aspirin. Since that year 19 children have been admitted after taking an average of 30 grains of this type of aspirin. Hyoscine, in the form of anti-

motion sickness tablets, has, since about the same time, joined the commonest substances taken. In this area ferrous sulphate is much less often a source of poisoning than in the North. Poisoning with the anti-histamines is also rare. Table 7 illustrates these points. The suggestion that coloured tablets may be more attractive than white ones gains some support from this series. Of the 114 tablets listed, 65 were coloured, 45 were grey or white and in four the colour was not known. In the absence of information on the relative numbers of each available, however, no firm conclusion can be drawn as to why this was so. The only fatality in this series occurred in the following circumstances.

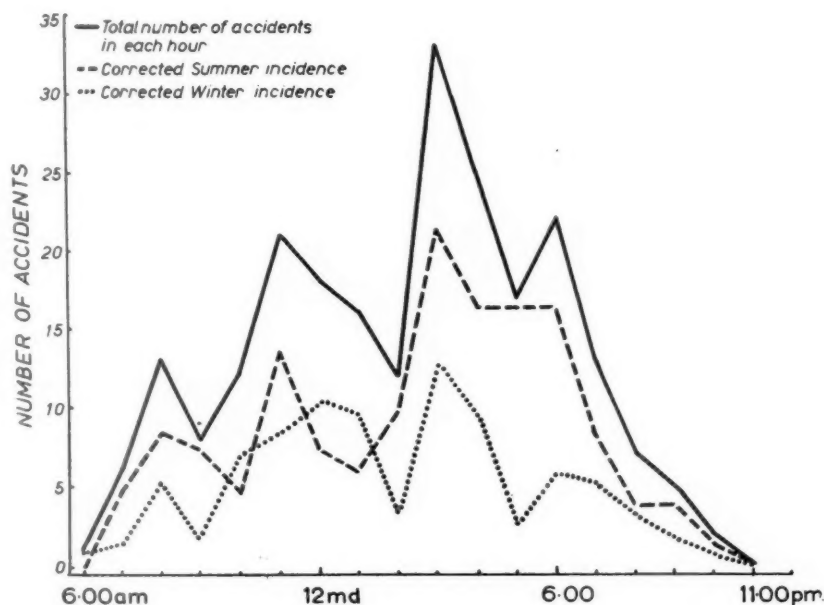


FIG. 2.—Distribution of poisoning accidents throughout day

The great disparity between the increases of accidental poisoning by medicaments and by household materials, clearly shown in the Scottish series, is not seen in this series. In fact, with the exception of 1955, each year has seen an approximately similar rise in both groups.

P.B., a boy aged 22 months, was admitted at about 11 a.m. He had been found one and three-quarter hours previously sucking some white tablets, at that time unidentified, which were kept in an unlocked medicine chest. On admission he was deeply cyanotic, unconscious and convulsing. Death occurred 40 minutes later.

The tablets were later found to contain iron and strychnine.

TABLE 5
ANALYSIS OF SUBSTANCES TAKEN

Substance	Number
(A) Medicaments for internal use	(126)
Aspirin of various types	36
Barbiturates	16
Laxatives	14
Ferrous sulphate, hyoscine of each	9
Anti-histamines, amphetamine, codeine, vitamin B preparations of each	4
Anti-convulsants, ephedrine, hypotensives, iron and strychnine, sulphonamides of each	2
Aconite tablets, digitalis, Dover's tablets, ephedrine and opium mixture, Eumydrin, linctus scillae, phenol mixture, Phosphorine, morphia and atropine tablets, stilboestrol, trinitrin of each	1
Unidentified tablets	2
(B) Medicaments intended for external use only	(37)
Camphorated oil	6
Surg. D.O.J. oint, liniments of each	4
Iodine, eye or ear drops, potassium permanganate crystals, antiseptics of each	3
Salicylic acid solution	2
Calamine, eucalyptus oil, flavine, formalin, Selsun, Stovarsol, T.C.P., tincture of arnica, contraceptive jelly of each	1
(C) Household materials	(96)
Disinfectants	17
Cleaning agents	5
Bleaching agents	14
Polishes	7
Turpentine	13
Paraffin	8
Petrol, paint of each	3
Hair shampoo, nicotine solution, soldering fluid, crayons of each	2
Brasso, camphor ball, cigarette, creosote, bath crystals, D.D.T. solution, dye, ink, ink powder, match heads, hydrochloric acid, paint remover, photographic developer, phosphorus rat poison, soda, solid fuel, artificial snow pellet, fir-tree oil of each	1
(D) Vegetable substances	(24)
Deadly nightshade berries	15
Woody nightshade berries	2
Laburnum seeds or pods	3
Other seeds or berries	4
(E) Unidentified or unrecorded	(2)
Total	(285)

Source of Poisons

Detailed information was sought from the parents of the last 150 children seen (i.e. all those seen after January, 1954) as to how and where the poisons were obtained. In about half these cases the enquiry was retrospective. Nine could not be traced and eight did not reply. There were five accidents each involving two children; these have been counted as single incidents.

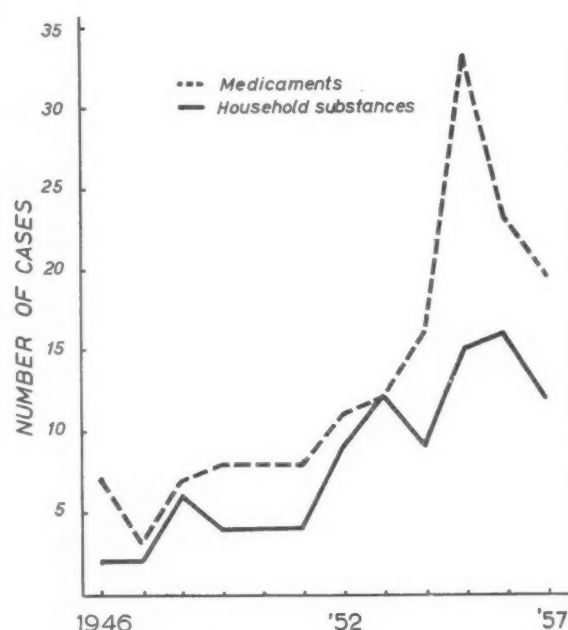


FIG. 3.—Annual incidence of poisoning accidents due to medicaments and household substances, 1946–57

TABLE 7
NUMBER OF ACCIDENTS DUE TO CERTAIN DRUGS, BY THREE-YEAR PERIODS, 1946–1957

Substance	1946–48	1949–51	1952–54	1955–57
Aspirin*	4	1	4	10
Baby type aspirin	0	0	5	14
Barbiturates	1	4	5	6
Laxatives	3	2	3	4
Iron	3	1	3	2
Hyoscine	0	1	4	4

* Including preparations with codeine

Room Concerned. The places in which poisons were obtained are listed in Table 8. In only 12 incidents was the poison obtained from a room other than that where it was normally kept. Comparison with two similar surveys made in the U.S.A. (Jacobziner and Raybin, 1956; Mellins *et al.*, 1956) shows that in this area comparatively fewer dangerous substances were obtained from bedrooms and kitchen, but more from the living rooms.

TABLE 6
ANNUAL INCIDENCE BY POISON GROUP

Substance	1946	1947	1948	1949	1950	1951	1952	1953	1954	1955	1956	1957
Tablets	3	3	6	5	4	6	7	9	13	21	14	18
All other medicaments	4	0	1	3	4	2	4	3	3	12	9	1
All medicaments	7	3	7	8	8	8	11	12	16	33	23	19
Household materials	2	2	6	4	4	4	9	12	9	15	16	12
Vegetable substances	0	1	2	4	4	1	1	4	0	3	2	2

TABLE 8
LOCATION OF POISONS

Place	Number
Kitchen	38 (26.2%)
Living and dining rooms	35 (24.1%)
Bedrooms	24 (16.5%)
Bathroom	8 (5.5%)
Sheds, garages, greenhouses	8 (5.5%)
Empty rooms, caravans, etc.	8 (5.5%)
Garden	10 (7.0%)
Not known or not recorded	14 (9.6%)

Site within Room. Within rooms there was considerable variation both as to where the poison was kept and where it was actually found (Table 9).

TABLE 9
NUMBER OF POISONS TAKEN BY SITE OF STORAGE AND SITE WHERE FOUND

	Drugs		Household Material	
	Normal-ly Stored	Found	Normal-ly Stored	Found
On tables, dressers, sideboards	6	17	5	21
Open shelves	8	6	16	7
Sills, mantel shelves, draining boards	2	9	1	3
Other open places	0	4	0	10
In cupboards	19	11	19	8
In bathroom or medicine cabinets	13	5	1	1
In drawers	10	9	0	0
No fixed place	4	—	0	—
Not normally kept in household	1	—	8	—
Information not available	19	15	7	4
The same as where stored		35		22
Different place		27		29
Not known		14		6

Excluded from this Table are (a) the vegetable group (7); (b) drugs given in error by parents from column 'Drugs Found' (6); (c) substances the sources of which remain unknown (3).

Clearly, one important factor in the aetiology of accidental poisoning is the frequency with which drugs and household materials are left easily accessible. Though there was a tendency to leave drugs in open positions temporarily rather than permanently, some strange places of storage came to light. A tin box on top of the television set, a dressing-gown pocket and a low, unlocked, glass-fronted cabinet were all used as medicine stores. In 11 of the 35 instances when a medicament was found in its normal place, there were other, sometimes more dangerous, substances present.

It is frequently stated that medicines kept under lock and key are safe from children. Of the 82 incidents involving medicaments, however, this good habit had been invalidated in 14 by various factors. Thus, two locked cupboards were opened, not by the children who took the medicaments, but by elder siblings who had found the keys. In one incident a drawer 'always kept locked' was for once left open,

and in four more the medicament was inadvertently 'left out'. Such situations may be ascribed to carelessness but the following are less easy to condemn. On three occasions drugs just bought were put temporarily with other contents of the shopping basket on the kitchen table before being locked up, only to be found within a few minutes by curious toddlers. Finally, four enterprising opportunists, aged from 11 months to 2 years, grabbed tablets within a few seconds of their being taken out for administration to others.

Height alone seemed to be of little protective value. Fourteen children obtained poisons from shelves or cupboards more than 5 ft. from the ground. No less than 40 are recorded as having climbed to reach the poison. Their average age of 2½ years is slightly less than that of the group as a whole, but boys outnumbered girls by three to one. Three of these children were aged less than 18 months. Perhaps the most ingenious climb was that of R.B. in Example 1.

EXAMPLE 1. R.B., aged 1 year 9 months, climbed up the ill-fitting and partly opened drawers of a dresser in a garden shed. Clinging on to the handles, he reached a bottle of soldering fluid on a shelf 6 ft. above ground.

Some of the value of relative inaccessibility is reduced when parents call medicinal tablets 'sweets' as an inducement to toddlers to accept them. The following examples illustrate some of the above factors:

EXAMPLE 2. S.C., aged 3 years, left his bed at 10 p.m., went into the kitchen, climbed with the help of a chair on to the dresser and opened a high wall cupboard. Ignoring seven other medicaments and disinfectants, he took a substantial amount of flavoured and coloured aspirin tablets. The mother had earlier in the day given him two of these 'sweeties' to help his cold. At the time of this incident both parents heard him but each assumed, being in different rooms, that it was the other who was opening the cupboard.

EXAMPLE 3. S.H., aged 1½ years, was given approximately 60 gr. of ferrous sulphate by her brother, aged 3 years, about 11.30 a.m. He brought a chair from the living room into the kitchen so that he could climb on to the dresser, having first found the key to unlock the top cupboard where mother kept her 'green sweets'.

Container. The variety of container from which the substances were taken was fairly restricted and is shown in Tables 10 and 11.

The pattern is similar to that reported by Mellins *et al.* (1956). On only 11 occasions had the substance been transferred from its original container to one less suitable. The proportion (7%) is much

TABLE 10
TYPES OF CONTAINER FROM WHICH POISONS WERE
TAKEN

Container	Number
Bottle	83
Plastic or glass tube	4
Tin	16
Cardboard box	25
Cup or open can	4
Envelope	2
No container	6
Not known	12

TABLE 11
TYPES OF CLOSURE OF CONTAINERS LISTED IN TABLE 10

Closure	Number
Screw cap	67
Cork	20
Plastic bung	2
Fit-over tin lid	4
Fit-in tin lid	3
No closure	10

Cardboard boxes, containers not designed to have lids and instances where there was either no container or where its nature was unknown have been excluded.

smaller than those recorded by Mellins *et al.* (1956) and Jacobziner and Raybin (1956), 40% and 30% respectively. Of these 11, eight involved paraffin or turpentine. It seemed significant that, of the nine bottles or jars without a lid, six contained one of these two substances. As paraffin or turpentine figured in a total of 14 incidents, it appeared that unusually casual handling of them was to some extent responsible for these accidents. This observation apart, study of the containers revealed little of importance. All the common types were represented. Frequently they are most unsafe. Dangerous drugs are supplied in envelopes or flimsy boxes; glass bottles are easily broken, especially when small hands reach high up to grip them; corks can be pulled out by toddlers' teeth when their fingers are not strong enough.

As might be expected, labelling was of little direct importance in the majority of poisoning accidents in young children. In the 14 incidents involving children over the age of 5 years, in only two was the substance labelled. In one instance the child was misled by the wrong label. Adequate labelling, however, ought to warn parents to take care in the storage of harmful substances, yet no less than 27 substances clearly labelled as dangerous were left easily accessible.

EXAMPLE 4. J.H., aged 2 years, took a plastic tube full of hyoscine tablets from a dressing table drawer which was never locked. Asked if the tube was labelled, father replied 'Yes, but it's of no consequence at his age'; yet the label stated 'CAUTION. It is dangerous to exceed the stated dosage'.

Labels such as the above were common. Very few stated unequivocally that the substance should be kept out of reach of children. Indeed one popular brand of analgesic bears a label stressing its safety and harmlessness without a warning of any kind; yet five children swallowed potentially harmful amounts.

Other Factors. Several other factors which occasionally operated are summarized below:

(1) Small children tend to be generous to each other. In this series 14 children were the innocent recipients of dangerous substances. The donors, 22 in number (for several incidents involved more than two children), ranged from 3 to 10 years of age and eight of them were over 7 years old. The older children acted thoughtlessly but not always stupidly and never with malicious intent.

(2) Parents may have their attention distracted by another child or visitor and leave dangerous substances within easy reach of youngsters. Seven examples of this were seen.

(3) Children visiting strange houses, which are normally without children, may become bored and wander away from adults to explore drawers or cupboards. This occurred four times.

(4) Whilst parents are moving house or decorating rooms medicines are apt to be left conveniently concentrated in one site, usually on the floor. This led to four accidents.

Conclusions

Nearly all these poisoning accidents occurred because the poison was too easily accessible to young children. Such a situation might be the result of several contributing factors; for example, inadequate furnishing and overcrowding in the home or curiosity, mischief and mental retardation in children. Much the most important factors, however, concerned the parents. Lack of appreciation of the exploratory abilities of children, ignorance of the danger of many household substances, carelessness and apathy in the use and storage of medicaments far outweighed truly accidental causes. This is illustrated by the summary of the causes of the 145 accidents investigated in detail (Table 12).

Though it might seem from this list that all the accidents in groups A to D (numbering 121 in all) could and therefore should have been prevented, this would assume a standard of knowledge, foresight and care far above that found in practice. In Examples 2 and 3 it would be difficult to accuse the parents of carelessness or stupidity. Study of the 120 accidents about which sufficient facts were known (excluding the garden group) suggested that

TABLE 12

HUMAN FACTORS CAUSING 145 POISONING ACCIDENTS

(A) Substance not in normal place of storage		
(1) Adult failed to replace it after use	50	
(2) Adult using it at time of accident	15	
(3) Adult distracted by other event whilst using substance ..	7	
(4) Family moving house; redecorating room	4	
(5) Substance just bought and not yet stored	3	
Total	79	
(B) Normal place of storage of substance inadequate		
(1) Exploratory ability of child not appreciated by parents	25	
(2) Insufficient supervision of child in strange house ..	4	
(3) Poisonous nature of substance not known to parents ..	1	
Total	30	
(C) Substance left in misleading container by parents ..	5	
(D) Substance given in error by parents	7	
(E) More than one of the above reasons	10	
(F) Curiosity of child in garden	7	
(G) Source of substance not known to parents	12	
(H) Information not available	17	

38 (32%) occurred without any obvious parental negligence. The other 82 (68%) seemed easily preventable.

Apart from trying to overcome adult apathy, several simple direct measures are possible. Greater use could be made of short but prominent labels such as 'Keep out of the reach of children'. This is already done by many pharmacists but might be more effective if manufacturers incorporated such a warning on all packages containing medicaments other than those which are harmless even in gross overdosage. Even laxatives can be fatal (Craig and Fraser, 1953). It would also be valuable if similar warnings appeared with the common household poisons such as disinfectants, cleaning and bleaching agents, paraffin and turpentine.

Some accidents would be prevented were the common and dangerous tablet poisons (aspirin, barbiturates, ferrous sulphate, hyoscine and the anti-histamines) always supplied in safety containers. These are merely small tins with snap-closing lids which young children are not strong enough to open. Unfortunately their relatively high cost would preclude their more extensive use. Finally, the tendency to store both medicaments and household materials in unsafe places might be reduced by providing safer storage facilities. Most new houses include several built-in cupboards. It would be neither difficult nor expensive to ensure that at least one in the kitchen and one in, say, a bedroom or the bathroom were fitted with a strong spring catch or similar safety device to defeat young hands.

Summary

The annual number of children accidentally poisoned in north-west Middlesex has greatly increased during the last 10 years. A study of 275 case histories over this period has shown that medicaments and household materials have contributed more or less equally to the rise.

The most susceptible age group was from 1½ to 2½ years of age. Relatively more accidents occurred during the summer months, the excess probably being due to longer daylight hours.

The commonest medicaments taken were aspirin, barbiturates, laxatives, ferrous sulphate and hyoscine. Disinfectants, bleaches, cleaning agents, turpentine and paraffin accounted for over half the household materials.

A more detailed study of 145 incidents showed that children obtained poisons from all parts of the house but most often from the kitchen and living room. Most of the substances taken had not been put away after use, were actually in use at the time, or were inadequately stored. Of this group, enough was known about 120 accidents to suggest that two-thirds could have been readily prevented and that these could be traced to the action (or lack of action) of adults. Predominant were carelessness in handling or storing materials and failure to appreciate the ability of children.

Easily applicable methods which might decrease the number of such accidents include more frequent use of warning labels on drug packages and on the commoner household poisons, greater use of safety containers and provision in all new houses of at least two safety cupboards.

I wish to thank Dr. H. V. L. Finlay for his generous advice and criticism and constant encouragement. I am also indebted to Dr. W. A. Steel for permission to publish this investigation and for the facilities which made it possible. Finally my thanks are due to his secretarial and records staff, particularly Miss M. Burley and Miss M. E. Bates, whose patience and help was much appreciated, and to Miss Beckett for producing the graphs.

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MEGALOBlastic ANAEMIA OF INFANCY IN JAMAICA

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Anaemia in infancy responding specifically to haemopoietic factors present in liver is not common. Between the years 1946 and 1953 a considerable number of cases was reported from the United States of America (Zuelzer and Ogden, 1946) and Italy (Amato, 1946; Pecorella, Burgio and Aversa, 1947). The literature up to 1953 is fully reviewed by Zuelzer and Rutzky (1953). Since that time reports have been rather rare (Freire, 1954; Mouriquand, 1954; Elizavéta, 1955; Morice, Gurzmán and Costa, 1955; Nelson and Creery, 1955; Amato and Di Gruttola, 1956; Gatto, 1957).

Much of the evidence suggests that megaloblastic anaemia of infancy is largely nutritional in origin, and it might therefore be expected that the disease would be common in those parts of the world where malnutrition is still rife. Protein malnutrition is widespread in Africa, the Far East, Mexico, South America and the West Indies (Trowell, Davies and Dean, 1954). Some degree of anaemia is usual in this disease, although an analysis of published material suggests that it is not as a rule severe in uncomplicated cases, since the haemoglobin level averages about 9.0 g.% (Table 1). The anaemia is

most commonly normocytic, although it may be microcytic or macrocytic (Altmann and Murray, 1948). It responds slowly to a protein-rich diet, and the response to liver, vitamin B₁₂ and folic acid has been described as 'poor, indefinite and erratic' (Trowell, 1949). The anaemia is commonly ascribed to protein deficiency associated with liver disease (Woodruff, 1955), although Gómez, Santaella, Galván, Cravioto and Frenk (1954) suggest that it can usually be attributed to an increase in plasma volume.

There have been few bone marrow studies in protein malnutrition. Trowell (1949) states that although at one time he thought that erythropoiesis was commonly megaloblastic, later he changed his opinion and now considers that erythropoiesis is usually macronormoblastic. Lambrecht and Holmans (1952) found some degree of erythroid hypoplasia but no megaloblasts in 24 cases. Woodruff (1955) found a macronormoblastic marrow in six cases. Altmann and Murray (1948) reported megaloblasts and giant stab cells in the marrows of a few of their cases, and Adams (1954) in Durban, South Africa, found megaloblasts in two out of 21 cases and giant stab cells and 'intermediate megaloblasts' in another six cases. Van der Sar (1951) reported one case with megaloblastic erythropoiesis which responded to folic acid. Kho Lien-Keng, Poesponegoro and Poey Seng Hin (1957) studied the bone marrow in 50 cases in Djakarta and reported occasional megaloblasts in six cases and giant stab cells, vacuolated granulocytes or hypersegmented neutrophils in another 26 cases. There was usually erythroid hypoplasia and the response to specific treatment was on the whole poor. Walt, Wills and Nightingale (1950) found no megaloblasts in 36 cases in Durban, but six years later they were able to report 42 cases of megaloblastic anaemia of infancy of whom just over half were also suffering from kwashiorkor (Walt, Holman and Hendrickse, 1956). The following year they described another 18 cases (Walt, Holman and Naidoo, 1957). In Sicily a condition has been described

TABLE 1
AVERAGE HAEMOGLOBIN LEVELS IN KWASHIORKOR

Author	Area	Cases (no.)	Mean Hb (g.%)
Altmann and Murray (1948)	Johannesburg	32	10.2
Walt, Wills and Nightingale (1950)	Durban	36	10.1
Van der Sar (1951)	Curaçao	33	9.3
Trowell and Davies (1952)	Uganda	44	8.5
Gómez, Santaella, Galván, Cravioto and Frenk (1954)	Mexico	51	9.3
Netrasiri and Netrasiri (1955)	Thailand	48	8.7
Woodruff (1955)	Nigeria	6	8.2
Poey Seng Hin (1957)	Djakarta	138	8.9

which resembles kwashiorkor very closely (Gerbasi and Burgio, 1955). It usually affects children under 2 years of age who suffer from diarrhoea, often of long standing, and skin changes, dryness of the hair, oedema and hepatomegaly. The liver often shows a severe fatty change, the serum proteins are low and anaemia is common and sometimes severe. Bone marrow studies showed megaloblasts in 10 cases and giant myeloid forms in 20 cases. The typical white cell changes of megaloblastic anaemia of infancy are well illustrated in their paper.

The purpose of this communication is to report 50 cases of megaloblastic anaemia of infancy seen between May, 1956, and November, 1958, and to emphasize that the disease is a common one in Jamaica.

Methods

Standard haematological methods were used (Whitby and Britton, 1957). *In vitro* sickling tests were carried out using a 2% solution of sodium metabisulphite (Daland and Castle, 1948).

Bone marrow was aspirated under local anaesthesia, using an Osgood (16 gauge) needle. The site of puncture selected was the upper end of the tibia about 2 in. below the tibial tuberosity. The marrow films were stained by both Leishman's method and the May-Grünwald-Giemsa technique. A portion of the aspirated material was allowed to clot in the syringe, and the specimen so obtained was fixed and sectioned histologically as described by Mertens (1945). The sections were stained with haematoxylin and eosin, and for iron by the prussian blue technique of Perls. All the sections were stained for iron simultaneously to minimize technical errors.

Results

The age distribution follows closely the pattern of kwashiorkor (Fig. 1) and, of the 50 cases, 32 were boys and 18 girls. Fever, vomiting and diarrhoea were the most common complaints and upper respiratory tract infections were frequent. On examination the most striking finding was that all the children were underweight and many severely so. This is represented graphically in Fig. 2 where the children's admission weights are compared with standard curves based on studies of child health and development made by the Department of Maternal and Child Health, Harvard School of Public Health (Nelson, 1950). In only one instance (Case 12) did the admission weight exceed the third percentile, but even in this case the figure was well below the mean (50th percentile) in the Boston series. Other stigmata of malnutrition were also found; some degree of oedema was present in 30 children, dyspigmentation of the skin was seen in 14 cases, and hair changes were found in 35 cases. The liver was readily palpable in 44 cases and grossly enlarged in seven of these. The spleen was palpable in five instances, but three of these cases also had sickle cell anaemia. Two other cases of sickle cell anaemia were seen and these five infants with sickle cell anaemia and associated megaloblastic anaemia are reported elsewhere (MacIver and Went, 1960). Extreme pallor of the palms of the hands, soles of the feet and mucous membranes was usually present. In summary all the infants in this series were suffering from malnutrition, which ranged clinically from

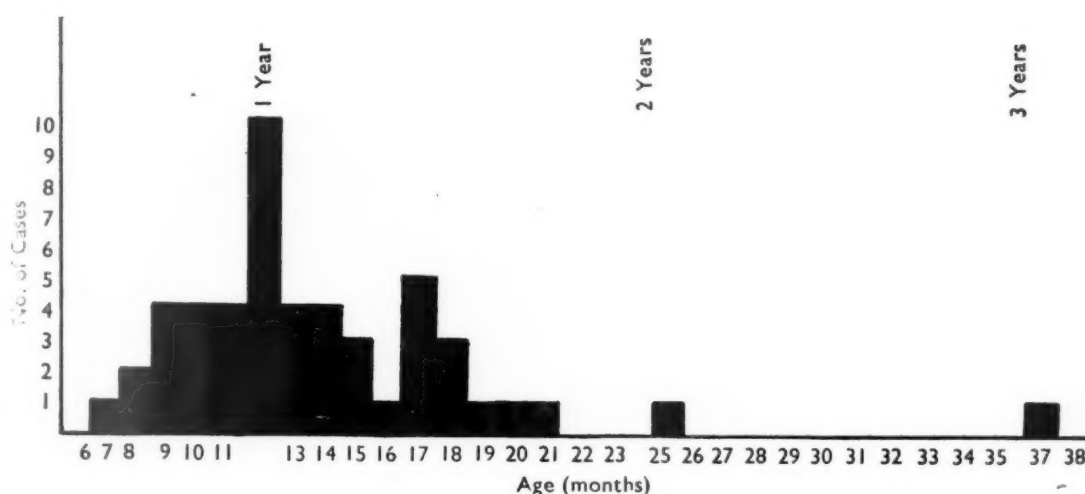


FIG. 1.—Age distribution of 50 cases of megaloblastic anaemia in infancy

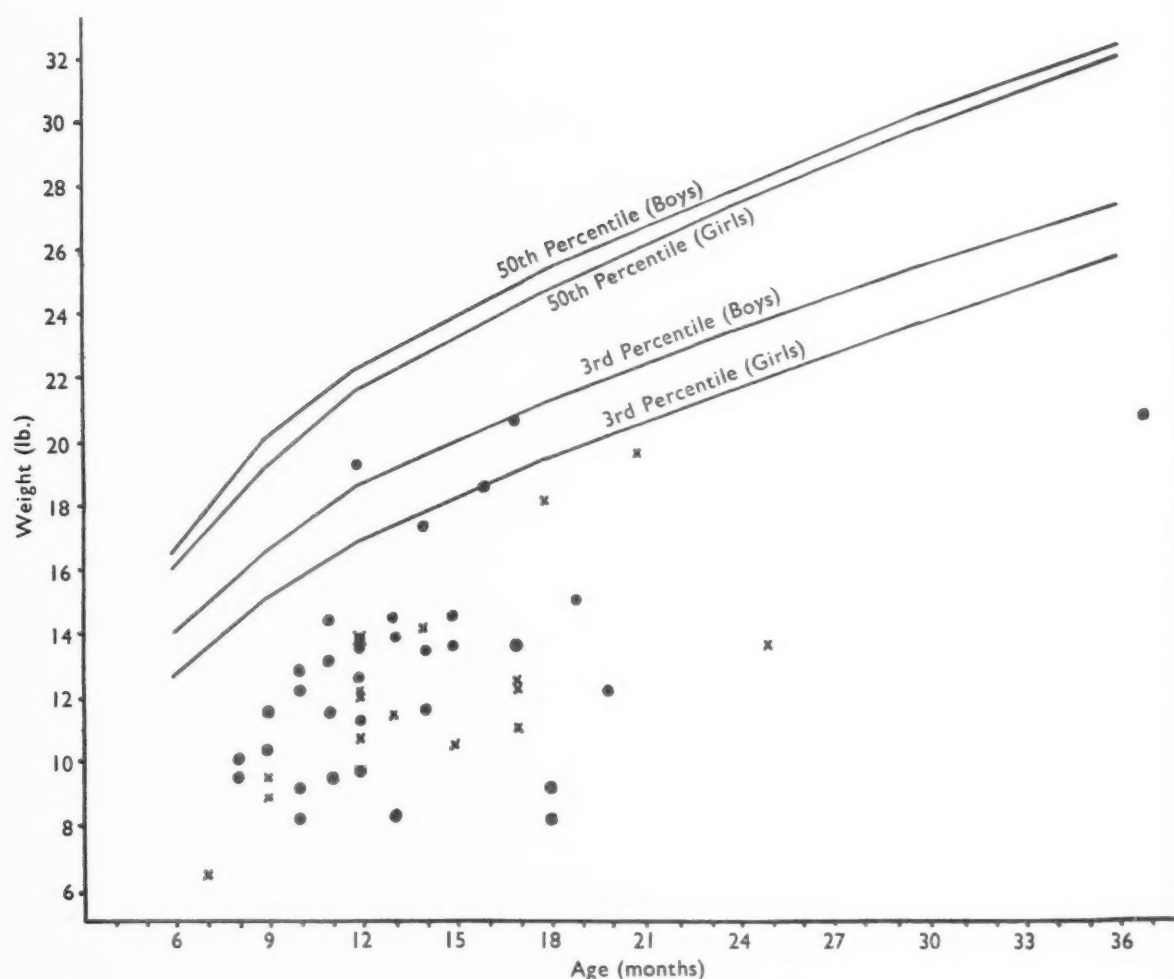


FIG. 2.—Admission weights of 50 cases of megaloblastic anaemia of infancy arranged by age as compared with standard curves for third and fiftieth percentiles prepared by the Department of Maternal and Child Health, Harvard School of Public Health ● boys × girls.

classical kwashiorkor in a few cases to a more marasmic picture in the majority.

The haemoglobin levels on admission ranged from 1.4 to 12.2 g.% but the great majority were very low (average 5.4 g.%). The few cases with high haemoglobin levels on admission developed anaemia in the course of treatment for malnutrition and bone marrow examination was rarely performed until the haemoglobin level had fallen to 7.0 g.% or less. The anaemia was usually normocytic and normochromic in type. Only occasionally was it definitely macrocytic (e.g. Case 48), but sometimes it was hypochromic. The reticulocyte count on admission was normally low, often below 1% (average 2.3%). The serum albumin level was usually low, ranging from 1.2 g.% to 4.4 g.% (average 2.5 g.%). Stool cultures were performed in the great majority of

cases: *S. typhimurium* was isolated in three instances (Cases 8, 9 and 34), *S. St. Paul* was found once (Case 14), pathogenic *Esch. coli* was isolated in five cases (type 0111 in Cases 3 and 29, type 055 in Case 8 and type 026 in Cases 14 and 42) and *Sh. sonnei* was found in one instance (Case 43). Mantoux and V.D.R.L. tests were negative in all cases examined, and the stools were examined routinely for hookworm and other parasites but were negative in every case. Gastric acidity was tested in five cases following the injection of histamine. In two (Cases 45 and 47) some free acid was found, whereas in the other instances (Cases 43, 46 and 50) there was no free acid. Faecal fats were estimated in three cases. In two, normal values were obtained (3g. per 100g. dry faeces in Case 46 and 2.6 g. per 100 g. dry faeces in Case 43). In the other infant (Case 34) a

raised value of 36 g. per 100 g. dry faeces was found, but on follow-up the percentage of fat fell to 14 and then to 6.5 g.% as the child improved clinically. The bone marrow was studied in every case, although in one infant (Case 49) the aspiration was performed 64 hours, and in another (Case 50) 16 hours after the start of oral folic acid therapy. In the majority of instances the marrow was of greatly increased cellularity, although in a few it was hypocellular and fatty. The mean myeloid/erythroid ratio in the whole series was 1.9 to 1, which contrasts strikingly with the findings of Kho Lien-Keng *et al.* (1957) in Indonesia, who found an average myeloid/erythroid ratio of 13.4 to 1.

Bone Marrow Morphology

(1) **Erythropoiesis.** In many instances the picture was indistinguishable from that seen in pernicious anaemia in relapse, and erythropoiesis was frankly megaloblastic (Fig. 3). Not infrequently, however, although megaloblasts were present in sufficient numbers to make the diagnosis beyond dispute, the majority of the erythroblasts were intermediate in type in the sense used by Downey (1952). These are the 'intermediate megaloblasts' of Dacie and White (1949). In such bone marrows erythroblasts could be seen in every stage of abnormality from classical megaloblasts on the one hand, through a variety of intermediate stages to typical normoblasts. In some marrows (e.g., Cases 8, 27, 30 and 31) no classical megaloblasts were seen at all, and although the erythroblasts were still abnormal it was not possible to describe erythropoiesis as other than normoblastic. In such marrows it was still possible to recognize a specific and diagnostic abnormality in the myeloid cells.

(2) **Leucopoiesis.** The granulocyte precursors showed constant qualitative changes which were no less characteristic than those of the erythroblasts. They were usually large and of a bizarre shape. Often they were clearly immature, perhaps premyelocytes or myelocytes, and yet the nucleus had undergone lobulation, indentation and even segmentation. Precise classification was often difficult. Giant metamyelocytes and stab cells were the most easily recognized abnormality and were identical with those seen in pernicious anaemia (Fig. 4). Striking vacuolation of the abnormal myeloid cells was often present (Fig. 5). We agree with Zuelzer and Rutzky (1953) that so far as megaloblastic anaemia of infancy is concerned these white cell changes are pathognomonic. They were seen in every marrow in the series, and sometimes they were unmistakably abnormal even when no typical

megaloblasts could be found. In such cases a therapeutic test with folic acid produced a characteristic reticulocyte response and a sustained haematological improvement. There is no doubt that these changes in the granulocytes provide a sensitive and easily visualized indicator of the early stages of megaloblastic anaemia before the characteristic changes in the erythroblasts have become apparent. We have never seen these white cell changes in iron deficiency anaemia, as reported by Davidson (1952) and Lehmann (1955).

Pathology. Six infants out of the series of 50 died and necropsies were carried out on all of them. In general the findings were those which are typically seen in protein malnutrition in children under 2 years of age in Jamaica (Jelliffe, Bras and Stuart, 1954; Bras, Waterlow and DePass, 1956). An additional finding which was of interest was that extramedullary erythropoiesis was seen in the liver (Fig. 6) in three Cases (3, 28, 43). In two others (Cases 4 and 44) a severe chronic fatty change was present, and in Case 6 an acute fatty change was noted. The immediate cause of death was frequently anaemia and bronchopneumonia.

Liver biopsies were carried out on 12 other infants, and extramedullary erythropoiesis was noted in seven of the 10 biopsy specimens which were sectioned histologically (Cases 13, 15, 16, 21, 22, 23 and 36). A severe chronic fatty change was seen in Cases 16, 23, 29 and 38.

We regard the finding of extramedullary erythropoiesis in the liver as a very characteristic feature of the disease since it has not been observed in several hundred necropsy and liver biopsy specimens from children with malnutrition in Jamaica, unless there was an associated megaloblastic anaemia. It is not, however, always present, and may be difficult to see or completely absent if the liver is very fatty.

Response to Treatment

Of the 50 cases in the series 45 were treated with folic acid and five received vitamin B₁₂. Six of the folic acid-treated cases died. The response to treatment is summarized in Table 2.

Folic Acid Therapy. The response to oral folic acid (5 mg. b.d.) in the 39 patients who recovered was uniformly excellent (Fig. 7). Within one or two days of starting treatment a striking clinical improvement was frequently noted. The increase in appetite and diminution of apathy were very marked and often preceded the reticulocyte response. Vomiting and diarrhoea, which had sometimes persisted for several weeks, were usually brought under control within a few days. A maximum reticulocyte response was

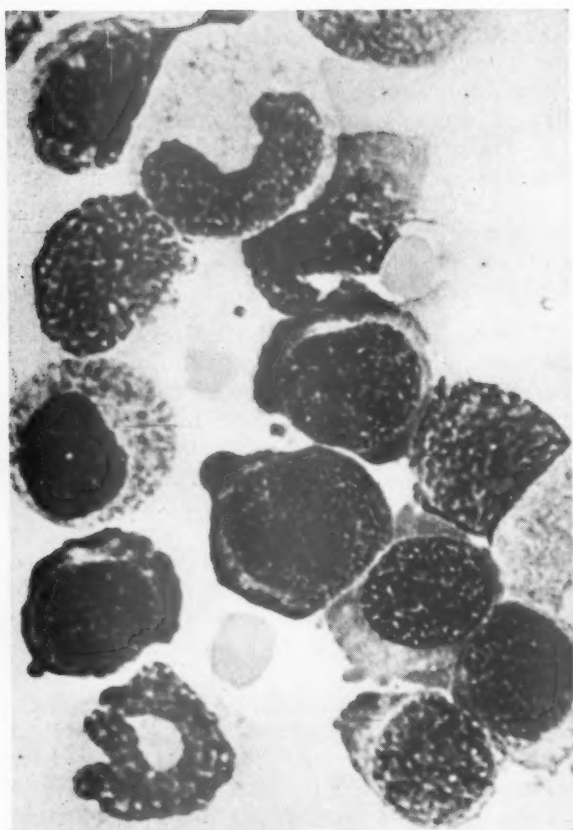


FIG. 3.

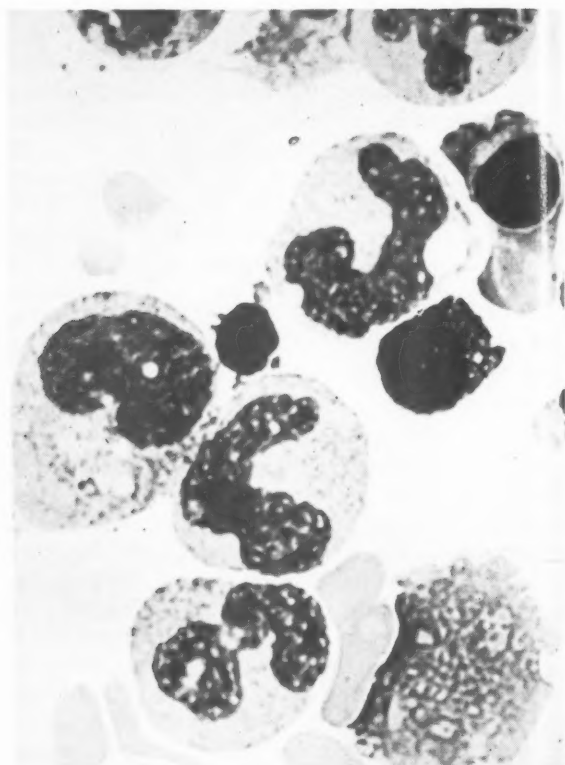


FIG. 4.

FIG. 3.—Bone marrow from Case 13. ($\times 1200$)

FIG. 4.—Bone marrow from Case 13 showing giant metamyelocytes and giant stab cells. ($\times 1200$)

FIG. 5.—Bone marrow from Case 6 showing vacuolated granulocytes. ($\times 1200$)

FIG. 6.—Necropsy section of liver from Case 3 showing extensive extramedullary erythropoiesis. ($\times 225$)

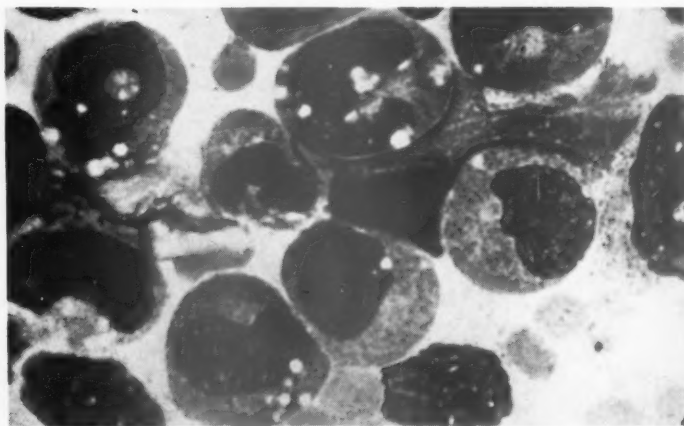


FIG. 5.

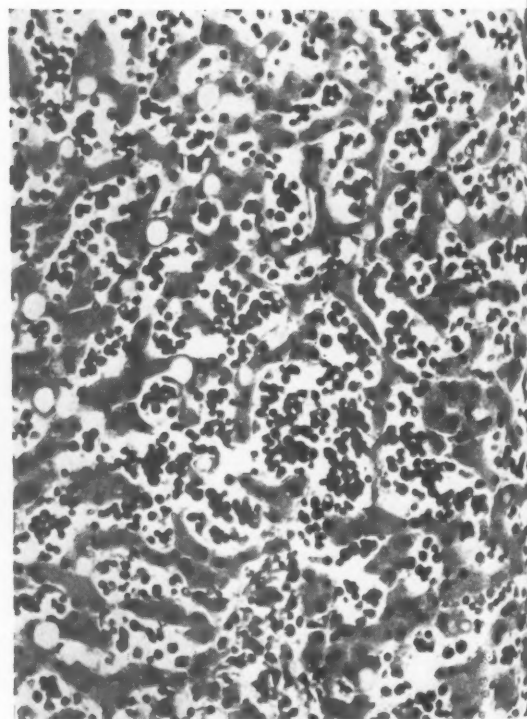


FIG. 6.

TABLE 2
RESPONSE TO TREATMENT (10 MG. FOLIC ACID DAILY, UNLESS OTHERWISE SPECIFIED)

Case No.	Hb (g.%)		Reticulocyte Count at Start of Treatment	Max. Reticulocyte Response (%) and Day after Start of Treatment	Max. Hb Level (g.%) and Day after Start of Treatment	Comments
	On Admission	At Start of Treatment				
1	4.2	4.0	5	17 (5)	10.1 (22)	Transfused (180 ml.) on admission Died suddenly after two days' folic acid therapy Transfused (130 ml.) Died after four days' folic acid therapy
2	2.3	7.5	1	10 (4)	10.1 (9)	
3	3.2	—	2	—	—	
4	3.2	—	0.1	—	—	
5	9.3	6.0	2	20 (9)	8.6 (16)	Died; congenital valve of urethra, pyonephrosis and peritonitis
6	2.8	—	0.2	—	—	
7	9.1	5.4	0.5	8 (7)	12.0 (29)	<i>S. typhimurium</i> and pathogenic <i>Esch. coli</i> (type 055) infections
8	12.2	6.3	0.5	6 (12)	9.5 (12)	
9	12.4	8.6	1	21 (4)	12.7 (11)	<i>S. typhimurium</i> infection
10	5.2	8.3	4	25 (8)	13.3 (24)	Transfused (150 ml.) on admission
11	4.1	6.2	9	32 (7)	8.2 (7)	Also had sickle cell anaemia
12	3.6	3.6	2.5	46 (4)	5.9 (13)	Also had sickle cell anaemia
13	1.4	1.4	0.1	19 (6)	9.4 (12)	Transfused (100 ml.) on admission
14	6.0	6.0	1.0	26 (10)	12.0 (48)	<i>S. St. Paul</i> infection; also pathogenic <i>Esch. coli</i> (type 026)
15	4.9	4.5	0.3	19 (7)	10.5 (31)	Treated with vitamin B ₁₂ , 50 µg. weekly
16	4.7	4.6	—	68 (3)	12.4 (27)	Reticulocyte count 19% two days after start of folic acid therapy
17	4.5	4.5	0.2	28 (8)	12.1 (38)	Treated with single dose of vitamin B ₁₂ (100 µg.)
18	1.8	8.3	1	20 (8)	10.4 (14)	Transfused (250 ml.) on admission; treated with single dose of vitamin B ₁₂ (1,000 µg.)
19	5.6	4.5	2.3	53 (5)	10.9 (18)	Transfused (150 ml.) before first Hb estimation
20	4.7	4.5	2	26 (6)	10.9 (33)	
21	4.5	3.2	2	24 (7)	9.0 (23)	Treated with single dose of vitamin B ₁₂ (1,000 µg.)
22	4.9	6.6	1	49 (5)	9.2 (19)	Also had veno-occlusive disease of liver
23	5.2	7.1	1.2	16 (4)	10.6 (12)	Transfused (125 ml.) four weeks after admission
24	2.7	2.7	0.5	41 (5)	12.2 (39)	Also had sickle cell anaemia
25	6.3	5.0	0.4	50 (15)	8.0 (27)	
26	5.0	5.0	2	37 (5)	9.9 (20)	Transfused twice (170 ml.; 150 ml.); died on third day of folic acid therapy
27	6.8	5.9	1.5	23 (5)	10.7 (21)	
28	3.8	4.8	0.1	—	—	Gastro-enteritis due to pathogenic <i>Esch. coli</i> (type 0111), treated with vitamin B ₁₂ (20µg. on alternate days)
29	8.0	6.5	5	34 (12)	12.5 (47)	Transfused (220 ml.) on admission
30	7.0	5.4	4	28 (5)	11.9 (42)	
31	4.3	4.3	11	21 (5)	12.7 (36)	<i>S. typhimurium</i> infection; also developed scurvy
32	5.8	5.8	3.8	19 (4)	14.4 (53)	Transfused (140 ml.) on admission
33	2.8	9.8	0.6	17 (7)	10.4 (7)	
34	11.2	6.2	1	41 (5)	13.0 (65)	Transfused three times in first week (180, 90, 180 ml.)
35	6.6	7.1	2	24 (3)	7.2 (5)	
36	1.8	6.5	5	28 (5)	11.9 (45)	Reticulocyte count 11% four days after start of folic acid therapy
37	4.6	4.6	1.6	32 (7)	11.5 (25)	
38	10.7	6.5	1	31 (5)	12.2 (26)	Gastro-enteritis due to pathogenic <i>Esch. coli</i> (type 026)
39	2.3	7.0	1	24 (11)	9.5 (15)	
40	7.3	7.5	1	19 (7)	11.2 (37)	Died after nine days' folic acid therapy
41	2.7	2.7	—	37 (10)	9.6 (16)	Transfused twice (100 ml.; 125 ml.); <i>Sh. sonnei</i> infection
42	11.2	6.2	1	35 (4)	12.2 (56)	Died on third day after one day of folic acid therapy
43	4.4	5.7	2.2	14 (7)	6.2 (7)	Also had sickle cell anaemia
44	5.0	—	0.1	—	—	
45	7.5	7.0	4	35 (12)	11.8 (31)	Reticulocyte count 30% three days after start of folic acid therapy
46	3.2	6.9	4.8	59 (6)	9.4 (40)	Also had sickle cell anaemia
47	6.5	6.5	—	46 (5)	9.1 (16)	
48	3.2	3.2	12	30 (3)	6.7 (10)	Transfused (150 ml.) on admission
49	4.5	8.2	0.4	19 (15)	11.4 (42)	
50	3.8	3.8	1	38 (7)	11.2 (32)	

sometimes seen in as short a time as three days and occasionally, particularly in the presence of severe infection, took as long as 15 days (mean six days). The rise in haemoglobin level after therapy was usually quite rapid, and in the 21 cases who received no blood transfusions the rate of increase in haemoglobin ranged from 0.08 g. per day to 0.37 g. per day (mean 0.2 g. per day).

Iron Therapy. Oral iron therapy was usually also required to achieve a sustained improvement, and in

fact some cases were demonstrably iron-deficient from the start as judged by a low mean corpuscular haemoglobin concentration, or more reliably by the absence of stainable iron in the bone marrow. Of the 31 cases in which the marrow was stained for iron, a positive reaction was obtained in 19, although in four of these only a trace of iron was seen. In seven cases ample iron was present (2, 6, 25, 34, 41, 43 and 47) but of these only Cases 6 and 47 had received no treatment before the marrow biopsy; Cases 2, 25 and 43 had been given blood transfusions,

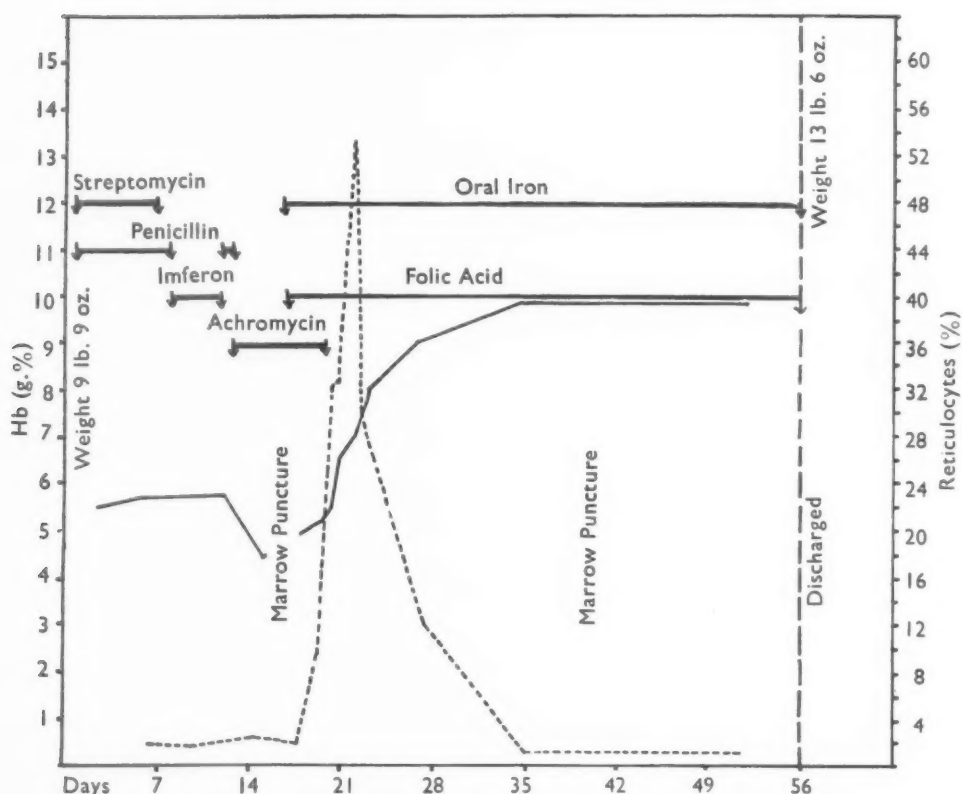


FIG. 7.—Chart of Case 19, aged 9 months, showing typical response to oral folic acid therapy. — Hb - - - reticulocytes

Case 41 had had two days of intramuscular iron and Case 34 had been on oral iron therapy for over three weeks. However, it is noteworthy that in no case was haematological improvement seen on iron therapy alone, and in fact in several instances the infant had been on iron therapy for some time before the marrow was examined, but in spite of that had continued to go downhill. Case 7 received 5 ml. of Imferon but nevertheless the haemoglobin level fell from 9.1 g.% on admission to 5.4 g.% in 38 days. Case 9 was on oral iron whilst the haemoglobin level fell 2.4 g.%, and Case 34 had been on oral iron therapy for 23 days when the marrow was examined, and during this period the haemoglobin level had fallen 2.1 g.%.

Vitamin B₁₂ Therapy. All five cases receiving intramuscular vitamin B₁₂ had a completely satisfactory haematological and clinical response. The dosage varied but was usually on the high side. Case 15 received 50 µg. a week for eight weeks, Case 29 was given 20 µg. on alternate days up to a total of 220 µg. and in the other three cases (17, 18 and 21) a single injection of 1000 µg. was given.

Antibiotics. A high proportion of the infants

were febrile on admission, and many had bronchopneumonia or gastro-enteritis. As a consequence, penicillin and achromycin were not uncommonly given during the first weeks after admission. Since nutritional megaloblastic anaemia in adults sometimes responds to penicillin (Foy, Kondi and Manson-Bahr, 1955), a response in infants might be anticipated. However, in no case was a response observed which could be ascribed to the antibiotic treatment, and in a number of instances the bone marrow aspiration was performed after prolonged use of antibiotics and erythropoiesis was none the less megaloblastic.

Discussion

Megaloblastic anaemia of infancy is a common condition in Jamaica and in 1957 6.3% of all admissions to the paediatric ward of the University College Hospital suffered from the disease. It is clearly a deficiency state, but the origin of the deficiency and what factor or factors are concerned in this deficiency is much less obvious. The ultimate biochemical defect may be of folic acid or its analogues, vitamin B₁₂, or other factors as yet unknown, and the deficiency need not necessarily be the

same in each case. The fact that all reported cases have responded to folic acid, as have all the surviving cases treated with this substance in the present series, does not prove that the deficiency is one of folic acid. The response to vitamin B₁₂ in megaloblastic anaemia of infancy has been more variable; all the children treated with it in the present series responded well, although the dosage in some cases was very high and, according to Frazer (1958), all megaloblastic anaemias will respond to vitamin B₁₂ provided the dosage is high enough. Other workers have reported satisfactory responses (McPherson, Jonsson and Rundles, 1949; Sturgeon and Carpenter, 1950; Zuelzer and Rutzky, 1953) although in some cases the response has been poor (Luhby and Wheeler, 1949; Zuelzer and Rutzky, 1953).

One of the most remarkable things about the history of megaloblastic anaemia of infancy is the almost meteoric rise and fall in the incidence of the condition in the United States. The flood of cases reported in that country between 1946 and 1953 may in part have been due to a 'high index of suspicion', but the virtual disappearance of the disease since 1953 is more difficult to explain. Considerable light was thrown on the aetiology of megaloblastic anaemia in infancy by the work of May and his associates, who undertook a series of experimental investigations on monkeys and showed that a megaloblastic anaemia could readily be induced in these animals by a diet of milk, which has a low content of folic acid, from which ascorbic acid has been excluded (May, Nelson and Salmon, 1949; May, Nelson, Lowe and Salmon, 1950; May, Sundberg and Schaar, 1950; May, Sundberg, Schaar, Lowe and Salmon, 1951; May, Stewart, Hamilton and Salmon, 1952; May, Hamilton and Stewart, 1953; Sundberg, Schaar and May, 1952). In considering the possible causes of folic acid and vitamin B₁₂ deficiency they concluded that 'a chronic deficiency of ascorbic acid leads to a deficiency of folic acid or some difficulty in the metabolism of folic acid or related compounds which results in a megaloblastic pattern in the marrow.' As evidence for this view they cited the high frequency of scurvy (25%) in the case reports of Zuelzer and Ogden (1946) and Aldrich and Nelson (1947).

As a result of the work of May and his associates, the manufacturers introduced large quantities of ascorbic acid (50 mg. per reconstituted quart) into milk formulas which had previously been associated with a rather high incidence of megaloblastic anaemia of infancy (Luhby and Wheeler, 1949), and it is probable that the virtual disappearance of the disease in the United States may, in part at least, be ascribed to this fact. In this connexion it is of interest that

in Zuelzer's last published series of cases (Zuelzer and Rutzky, 1953) milk foods, which had been modified by the sole addition of ascorbic acid, disappeared from the history of infants with megaloblastic anaemia, whereas an unmodified brand persisted.

The importance of ascorbic acid deficiency in the aetiology of the disease in the present series is difficult to evaluate. In only one instance (Case 34) was frank scurvy noted and the deficiency became manifest after the child had been in hospital for 78 days. The infant was malnourished on admission but was not particularly anaemic, even taking into account the dehydration which was present. He had severe gastro-enteritis and *S. typhimurium* was isolated from the stools. Despite courses of achromycin and chloramphenicol the diarrhoea persisted and the *Salmonella* was again found. The child was on a milk diet with the addition of small quantities of orange juice during this period, but the haemoglobin fell steadily from 11.2 g.% to 6.4 g.% after 55 days (Fig. 8). A bone marrow examination at this time showed megaloblastic erythropoiesis, and folic acid was given. A good reticulocytosis and some rise in haemoglobin followed, but soon afterwards the haemoglobin level began to fall again. Clinical evidence of scurvy then appeared and treatment with ascorbic acid (the folic acid was still continued) produced a second reticulocyte response of 20% and a rapid rise in haemoglobin level. In this case there can be no doubt about the importance of ascorbic acid in the proper utilization of folic acid, but, since scurvy is very rarely seen in Jamaica, it is difficult to believe that a deficiency of ascorbic acid can be of aetiological significance in the majority of cases in this series.

There is little doubt of the important part played by infection in the causation of the disease. May *et al.* (1952) were able to produce megaloblastic anaemia in monkeys on a milk diet with adequate amounts of ascorbic acid by inducing turpentine abscesses. It is probable that infection increases the requirements for ascorbic acid. In the present series infections were extremely frequent. A history of recent upper respiratory tract infections or chest colds was elicited in 26 cases, and gastro-intestinal infections were common. Vomiting had occurred in 37 cases, and diarrhoea in 29. As mentioned earlier, specific pathogens were isolated from the stools in several instances, and the importance of gastro-intestinal infections in the aetiology of megaloblastic anaemia is well illustrated by the following case.

Case 9. This 9-month-old infant was admitted with a history of vomiting after feeds for one week and diarrhoea

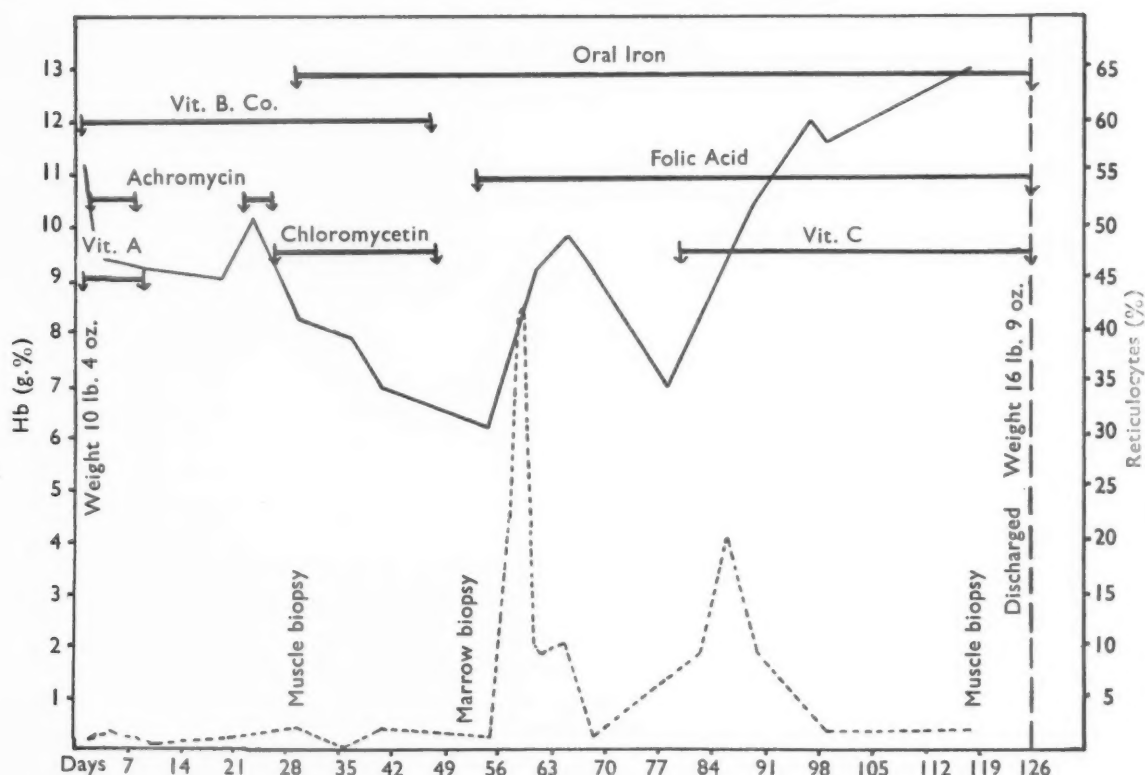


FIG. 8.—Chart of Case 34, aged 8 months, showing fall in haemoglobin level associated with *S. typhimurium* infection, response to folic acid and second response to ascorbic acid (see text). — Hb - - - - reticulocytes

for three days. His nutritional state was moderate. *S. typhimurium* was isolated from the stools and despite a course of chloramphenicol the same organism was found again two weeks later. During the course of the first four weeks the haemoglobin level fell from 12.4 g.% to 6.7 g.% (Fig. 9) and, despite treatment with penicillin and streptomycin, he had continual fever. A blood transfusion was given but the haemoglobin level fell again rapidly. On the forty-sixth day the bone marrow was examined and found to be megaloblastic. Treatment with folic acid produced a dramatic result both clinically and haematologically for not only was there a good reticulocyte response and haemoglobin rise, but the fever settled almost immediately and did not recur.

A similar rapid fall in haemoglobin level in infants with gastro-enteritis was observed in Cases 8, 34 and 42.

The mechanism by which gastro-intestinal infections predispose to the development of a megaloblastic anaemia is probably rather complex. In the first place there is the factor of the infection itself, which has already been discussed. Secondly, anorexia and vomiting are frequently associated so that the intake of haemopoietic factors is reduced.

Thirdly, the absorption of these haemopoietic factors may be impaired as a result of persistent diarrhoea. Fourthly, the abnormal bacterial flora in the intestine associated with the infection may lead either to an increased bacterial utilization of these factors or to a reduced synthesis of them.

However important infection and ascorbic acid deficiency may be in the causation of megaloblastic anaemia of infancy, there can be little doubt that the main factor responsible in our series is a dietary deficiency of essential haemopoietic substances. All the infants in the series were underweight, and many were severely so. In addition the features of protein malnutrition were often present. In Table 3 are summarized the diets of the infants in this series, and they are clearly grossly inadequate. Milk, which is the chief staple of an infant's diet during the first year of life, has a low folic acid content, and the heating processes, such as those involved in the canning and powdering of milk, further reduce this small amount of folic acid (Luhby and Wheeler, 1949). Only a few of the infants received any fresh milk and the majority were given only very small

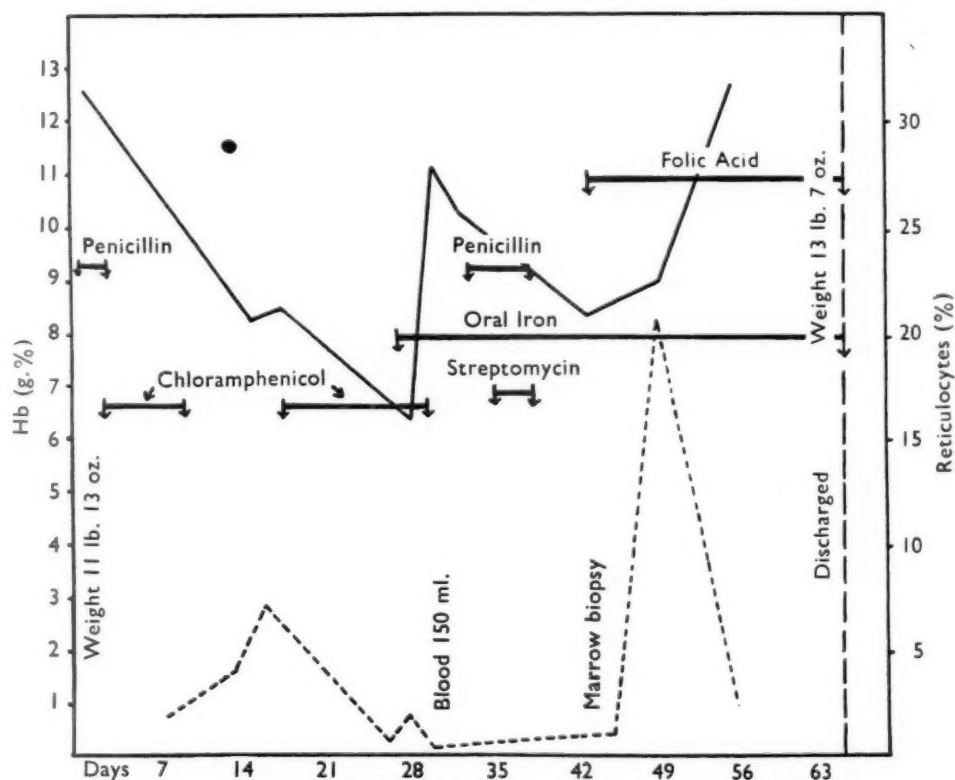


FIG. 9.—Chart of Case 9, aged 9 months, showing fall in haemoglobin level associated with *S. typhimurium* infection and response to folic acid. — Hb - - - - reticulocytes

TABLE 3
SUMMARY OF DIETARY HISTORIES

Case No.	Age (mth.)	Breast Feeding (mth.)	Type of Milk after Weaning	Cereals	Vegetables	Meat	Eggs	Orange Juice	Bush Teas
1	14	7	Skim	Oats	Cho-cho; potatoes	—	Occasional	+	Mint
2	17	6	Skim 2 mth.; Ovaltine	Cornmeal	—	—	—	—	—
3	11	3	Condensed; goat's; skim	Oats	—	—	—	—	Love weed (dodder)
4	13	9	Cow's 2 mth. (none subsequently)	—	—	Beef tea	—	—	—
5	10	9	Lactogen; Cow and Gate	—	—	—	—	+	Love weed (dodder)
6	12	5	Condensed	Oats	—	—	—	—	Mint; Irish-moss (sea-weed)
7	25	9	Cow's	—	Carrot juice	+	+	+	—
8	10	2	Lactogen; Ostermilk; cow's	Cornmeal	—	—	+	+	Mint
9	9	7	Condensed; skim	Oats; arrowroot	—	—	—	+	Mint
10	7	3	Condensed	Barley water	Carrot juice	—	—	+	Irish-moss (sea-weed) linseed
11	12	3	Skim	—	Sweet potatoes; carrot juice	—	—	—	—
12	12	6	Condensed; occ. cow's	Cornmeal	—	Occasional	—	—	Mint
13	17	5	Condensed; occ. cow's	Arrowroot	Occasional	—	Occasional	+	Rosemary; mint
14	20	?	Occ. goat's	—	?	?	?	?	?
15	17	?	?	?	?	?	?	?	?
16	11	4	Skim	Barley water; Quaker oats	—	—	Occasional	+	—
17	12	2	Condensed; occ. powdered	Patent barley; cornmeal; Farex	—	—	—	—	—

(cont.)

TABLE 3—cont.

Case No.	Age (mth.)	Breast Feeding (mth.)	Type of Milk after weaning	Cereals	Vegetables	Meat	Eggs	Orange Juice	Bush Teas
18	18	6	Cow's; condensed	Occ. porridge	—	—	—	—	Jack-in-the-bush; susumber
19	9	5	Cow's	Farex	—	—	—	—	Various
20	12	9	Cow's; Ovaltine	Wheat; cornmeal	—	—	—	—	—
21	17	9	Skim; condensed; Cow and Gate	Cornstarch; barley	—	—	—	—	—
22	14	3	Cow's; condensed	Cornmeal	—	—	—	—	Cerosee; love weed (dodder); Jack-in-the-bush
23	13	12	Lactogen	Saltine biscuits	—	—	+	+	Various
24	18	3	Lactogen	Porridge	—	—	—	—	—
25	12	8	Condensed; Ovaltine; skim	Quaker oats	Sweet potatoes	—	Occasional	—	Mint; cerosee
26	17	5	Lactogen; cow's	Cornmeal	—	—	—	—	Mint
27	10	—	Skim; goat's since 5 mth.	Oats	Sweet potatoes	—	—	—	—
28	15	4	Cow's; Milo	Oats	Sweet potatoes	—	+	+	—
29	8	6	Cow and Gate; Ostermilk; condensed	—	—	—	+	+	Irish-moss (sea-weed); linseed
30	9	3	None 1 mth.; cow's 3 mth.; none last 2 mth.	Cornmeal; barley; cornstarch; arrowroot	—	—	—	*+	—
31	14	7	Skim	Oats	—	—	—	+	Mint; Jack-in-the-bush
32	12	9	Condensed	Porridge	Banana	Fish tea	—	—	—
33	21	8	Cow's	Wheat; rice	Yam; sweet potatoes	Fish	+	+	—
34	8	1	None 2 mth.; skim; cow's; condensed	Oats at 3 mth.	—	—	—	Occasional	Mint
35	10	6	Skim	Barley; oats	—	Fish tea	—	—	—
36	15	6	Cow's; Lactogen; skim	Barley; Bemax	—	—	—	—	Mint
37	11	6	Ovaltine; Milo; condensed	Oats; cornmeal; arrowroot	—	—	+	+	Mint
38	9	1	Various proprietary brands; none from 4 mth.	Cornmeal	Green banana	—	—	—	—
39	18	4	Lactogen; Ovaltine	Barley } from oats } 1 yr.	—	—	—	—	Cotton; susumber; mint; Irish-moss (sea-weed)
40	12	6	Lactogen; Horlicks; condensed	Cornmeal	Coconut milk	—	—	—	Milk-weed; negeu; vervine; love-bush; Jack-in-the-bush
41	37	?	Lactogen; } all cow's; } tried and refused; Ovaltine } still bottle fed	Barley water; porridge	Tried and refused	Tried and refused	Tried and refused	Tried and refused	—
42	13	—	Skim; condensed; Vita-cup	—	—	—	—	—	—
43	12	—	Horlicks; Cow and Gate; skim; goat's	—	—	—	—	—	Jack-in-the-bush; White Joseph's coat; God bush; mint
44*	11	?	Condensed; little or none for 3 mth.	Oats; cornmeal	—	—	—	—	—
45	16	10	Cow's; Lactogen	Oats	—	—	—	—	—
46	13	8	Lactogen; condensed; skim	Oats	—	—	—	—	Mint; cerosee
47	12	5	Condensed; skim	Barley water	Spinach; sweet potatoes; cho-cho	—	—	—	Mint
48	14	8	Ostermilk; Milo; condensed	Bread; biscuit	Sweet potatoes	Soup, fish tea	+	—	—
49	12	7	Cow's; Milo	Oats; sago	—	Fish tea	—	—	Mint
50	15	8	Lactogen; Cow and Gate	Barley	Carrot juice	Fish tea	+	—	—

* 3-day dietary survey at home showed intake of 400 calories and 0.75 g. protein per day

quantities of condensed or powdered milk. Goat's milk, which has an even lower folic acid content than human or cow's milk (May *et al.*, 1952), was included in the diet of four infants in this series (Cases 3, 14, 27 and 43). Supplementary foods rich in folic acid, such as meat and green vegetables, were almost totally absent from their diets, which con-

sisted largely of cereals, such as cornmeal, made into a porridge with small quantities of milk, supplemented with a variable quantity of carbohydrate-rich foods such as sweet potato, green banana, cassava and yam. The folic acid content of these foods is not known, but, with the possible exception of green bananas, it is not likely to be high. Vitamin B₁₂

is found in most animal tissues such as meat and eggs, but it is almost completely absent from higher plants. Milk contains a reasonable amount of vitamin B₁₂ but the quantity given to these infants was generally very small, one or two tins of condensed milk being required to last a week or more in most cases. It is therefore quite probable that the children were deficient in both folic acid and vitamin B₁₂, although it seems likely that deficiency of folic acid is the most important factor. In addition to the inadequate intake of haemopoietic substances, the children also received too little protein, and the results of protein malnutrition became manifest. Anorexia was usual and vomiting and diarrhoea were frequent so that the already small intake of haemopoietic substances was further reduced and absorption was impaired.

It is probable that the disease could be quickly eradicated in Jamaica if supplies of milk were more freely available and in particular if the mothers were educated to the importance of including some green vegetables and, if economically possible, meat in the diets of their children in the post-weaning period.

Summary

The literature on megaloblastic anaemia of infancy is briefly reviewed with particular reference to its occurrence in association with protein malnutrition (kwashiorkor).

The clinical, haematological and other laboratory findings in 50 cases of megaloblastic anaemia of infancy are presented. From a clinical point of view the most striking feature is that almost all the infants were very malnourished and grossly underweight. The bone marrow morphology is described, and the diagnostic value of specific changes in the granulocytic series is stressed.

An interesting pathological finding was the presence of extramedullary erythropoiesis in the liver. This was found at necropsy in three out of six cases, and on liver biopsy in seven out of 10 cases. Although not constantly present, extramedullary erythropoiesis is thought to be pathognomonic of the disease.

Of the 50 cases in the series 45 were given folic acid and five received vitamin B₁₂. Six of the folic acid treated cases died. The response to both folic acid and vitamin B₁₂ in the remaining cases was excellent. No response to antibiotics was noted. The pathogenesis of the disease is discussed in some detail and illustrated with cases. Although there is no doubt of the importance of ascorbic acid deficiency and of infection in the aetiology of megaloblastic anaemia of infancy, it seems probable that a dietary deficiency of essential haemopoietic factors is the major cause.

Whether the main deficiency is of folic acid or of vitamin B₁₂ is uncertain at the present time, although in our view a deficiency of folic acid seems likely to be the more important.

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CONGENITAL THROMBOCYTOPENIC PURPURA

BY

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The purpose of this paper is to present four cases of neonatal thrombocytopenic purpura which have been investigated fully. Although an uncommon condition, it has aroused a good deal of interest and nearly 100 instances have been recorded to date. The literature has been reviewed by Robson and Walker (1951), who collected 52 cases and added three of their own, and also by Morris (1954), who gives references for a further 27 cases and also describes three more under her care. A detailed account of the condition is to be found in Stefanini and Dameshek's text-book *The Hemorrhagic Disorders* (1955).

The original classification of patients with congenital thrombocytopenic purpura into two main groups by Robson and Walker is now generally accepted as a helpful and practical division and is as follows:

Group I.—Infants born of mothers with thrombocytopenic purpura

- (a) idiopathic type (I.T.P.), including mothers who had undergone splenectomy
- (b) secondary or symptomatic type due to drugs, infections, toxæmias, etc.

Group II.—Infants born of normal mothers

Nevertheless this classification may be artificial since there are several instances on record (Sanford, Leslie and Crane, 1936; Urbanski and Hutner, 1942; Finn, 1944) illustrating that a woman may suffer from idiopathic thrombocytopenic purpura (I.T.P.) but be symptom-free and in remission during pregnancy and yet give birth to a thrombocytopenic infant. Unless repeated maternal platelet counts are carried out post-natally, such a case may be incorrectly assigned to Group II. An affected mother may give birth to a normal child (Finn, 1944) or may have dissimilar twins, one affected and one not (Goldstein, 1947). It is also possible that in these congenital cases a genetic fault is sometimes responsible and that fathers as well as mothers could be involved.

A more elaborate classification based on aetiology and illustrating the widely different mechanisms to which congenital thrombocytopenia may be attributable is that of Stefanini and Dameshek (1955). In this, cases are divided into two main groups according to whether megakaryocytes are absent or markedly reduced in the bone marrow (amegakaryocytic), or present in normal or increased numbers (megakaryocytic):

Group I.—Amegakaryocytic

- (1) Congenital hypoplastic anaemia (including the Fanconi syndrome)
- (2) Congenital hypoplastic thrombocytopenia
- (3) Congenital acute leukaemia (usually granulocytic)
- (4) Sepsis, congenital syphilis, other infections, viral diseases, etc.

Group II.—Megakaryocytic

- (a) Children of non-thrombocytopenic mothers
 - (1) Idiopathic thrombocytopenic purpura (rarely present at birth)
acute variety
chronic variety
 - (2) Erythroblastosis foetalis
with demonstrable platelet agglutinins
without demonstrable platelet agglutinins
 - (3) Platelet type incompatibility between mother and foetus
- (b) Children of thrombocytopenic mothers
 - (1) Transplacental transfer of platelet agglutinins from mother to foetus (platelet agglutinins as a rule demonstrable in the mother's plasma)
 - (2) Drug thrombocytopenia (transfer through the placenta of both a platelet-destructive factor and the offending drug)

The four cases described in this paper were all the children of apparently healthy non-thrombocytopenic mothers.

Case Reports

Case 1. (Fig. 1.) Paul B., a male child, was delivered at full term. The mother had had rubella at the eighth week of pregnancy and a purpuric rash appeared on the child's trunk, face and limbs within 15 minutes of birth (Figs. 2 and 3). He had various congenital defects, including penile hypospadias, a heart lesion and a cataract. On the first day after birth the platelet count was 56,000/c.mm.; the bone marrow showed very scanty megakaryocytes (Fig. 4) and those present had an atypical lymphoid appearance and seemed indolent as regards platelet production (Figs. 5 and 6); erythropoiesis was active; no platelet agglutinins were demonstrable in the infant's serum nor in the maternal serum put up against the infant's platelets. The platelet count after some fluctuation fell to 36,000/c.mm. on the eighth day. On the following day prednisolone was commenced and there was a satisfactory response in the platelet count which rose to normal and has remained normal since. A second marrow examination carried out about one month after birth, whilst the platelets were increasing, showed numerous megakaryocytes of normal morphology (Fig. 7). This child showed no significant anaemia.

Case 2. (Fig. 8.) Andrea H., a female child, was born at full term. About six hours after delivery a petechial rash was noted, mainly on the face and in the skin creases but also scattered over the trunk and limbs. Her initial platelet count on the second day was 96,000/c.mm. The bone marrow on the third day showed a paucity of megakaryocytes; of those present some were of an intermediate type with granule formation whilst others were of the lymphoid variety, both devoid of platelet formation. Erythropoiesis was active. No platelet agglutinins were demonstrable in either the infant's or the mother's serum. The platelet count had dropped to 40,000/c.mm. by the fifth day when prednisolone was commenced. There followed a rapid rise in the platelet count which has remained normal. No anaemia was present.

Case 3. (Fig. 9.) Stella H., a second-born female child, was delivered at full term. Four days after birth she passed a small amount of blood per vaginam. Nine days after birth there was a large bruise on the left leg and it was noted that there was a tendency to bleed easily from a scratch over one eye. On the following day a small bruise appeared on the right leg. On the tenth

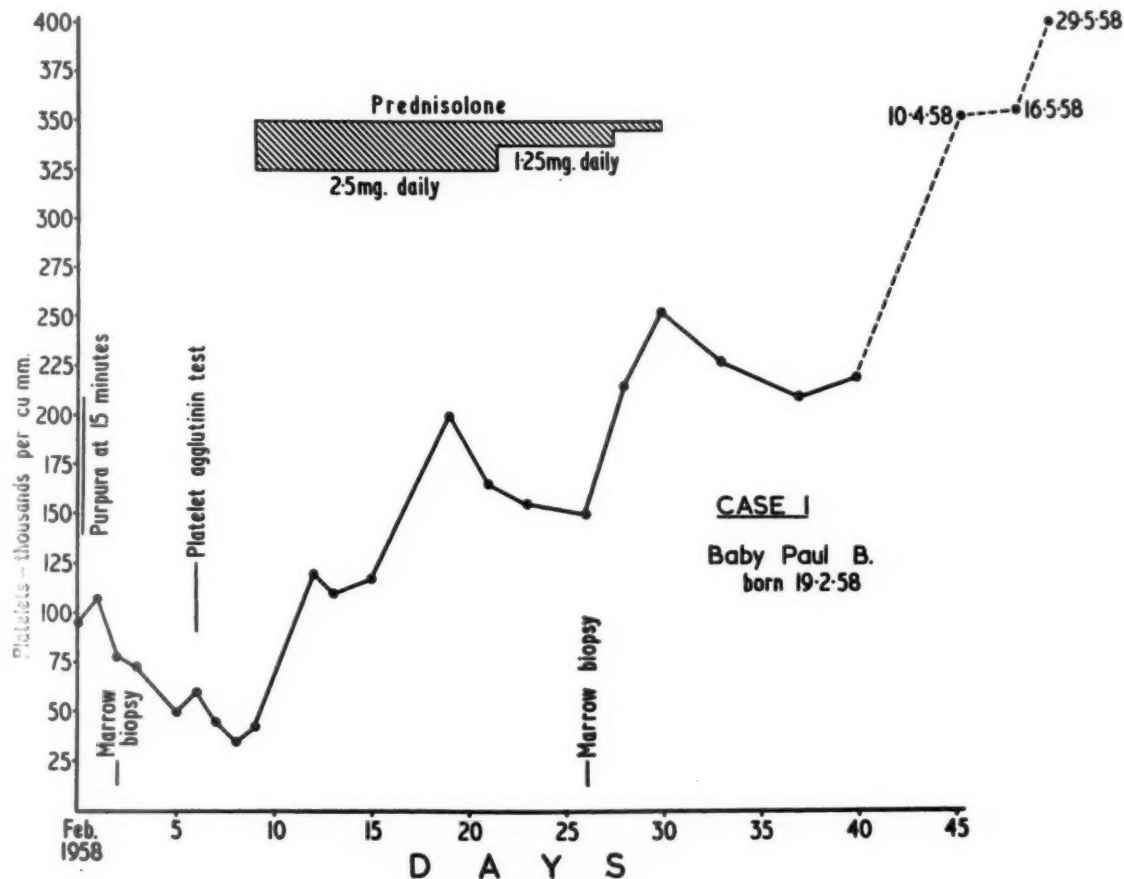


FIG. 1.—Case 1.



FIG. 2.



FIG. 3.

FIGS. 2 and 3.—Case 1.

FIG. 4.—Case 1. Smear of tibial marrow taken one day after birth. $\times 175$. (Marrow findings in Cases 2 and 3 during thrombocytopenic phase were similar.)

FIGS. 5 and 6.—Case 1. Drawing of 'intermediate' and 'lymphoid' types of megakaryocytes present in tibial marrow smear. $\times 800$.

FIG. 7.—Case 1. Smear of tibial marrow taken 26 days after birth when platelets had risen to 152,000 per c.mm. $\times 220$.

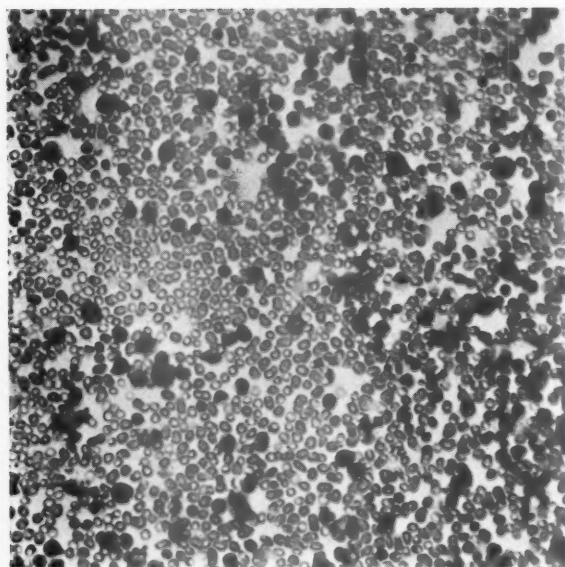


FIG. 4.

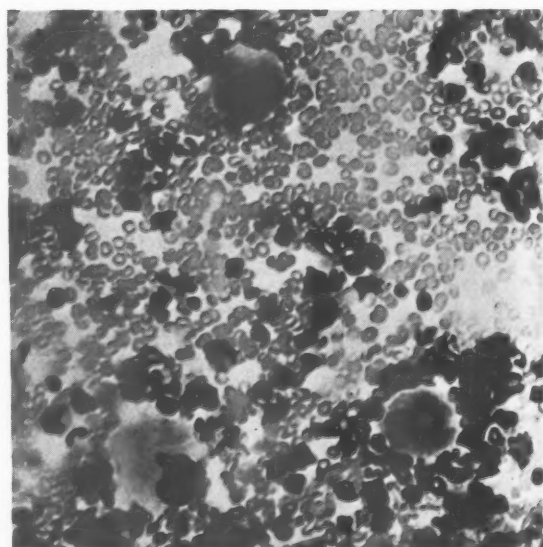


FIG. 7.

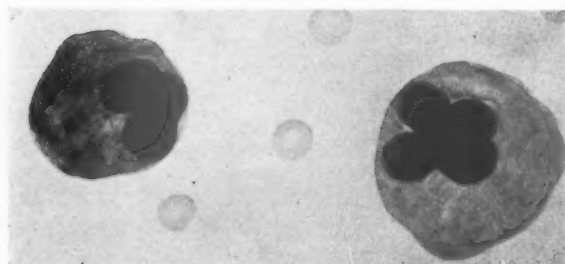


FIG. 5.

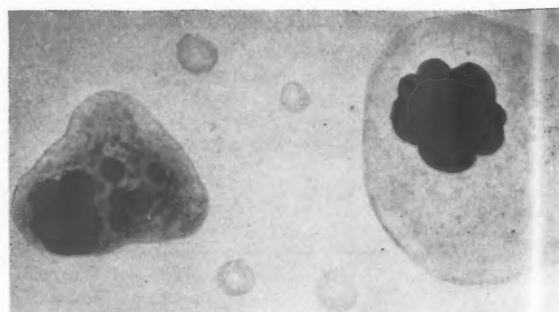


FIG. 6

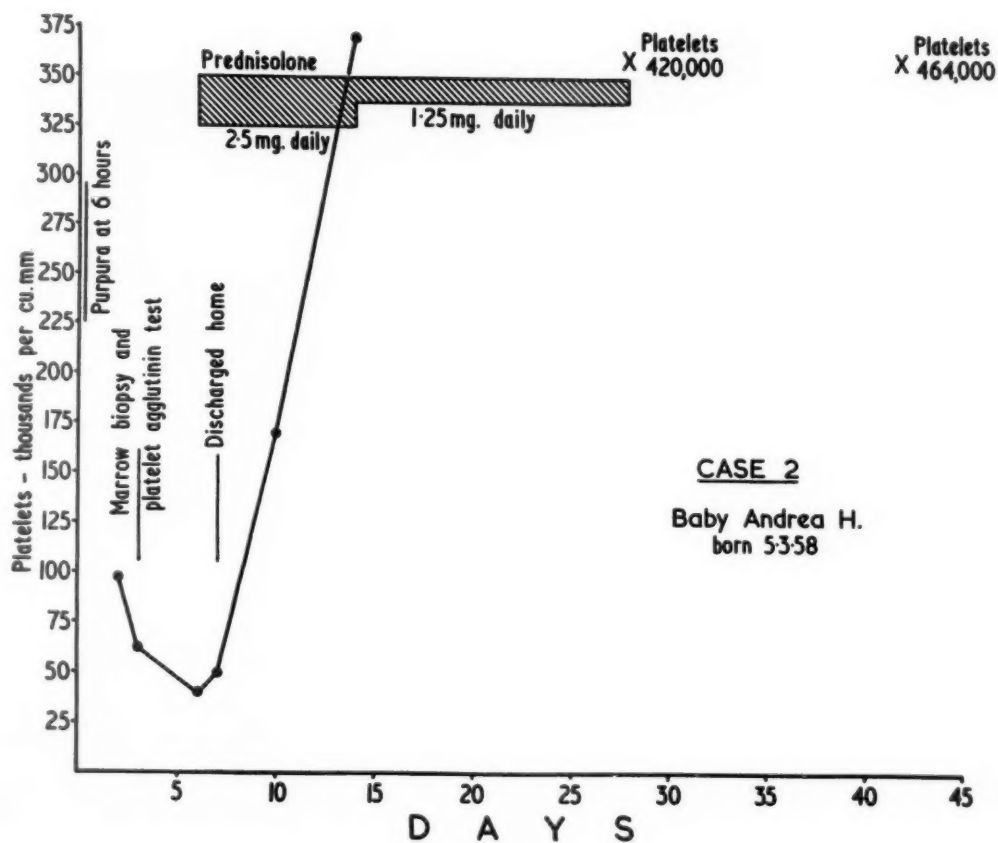


FIG. 8.—Case 2.

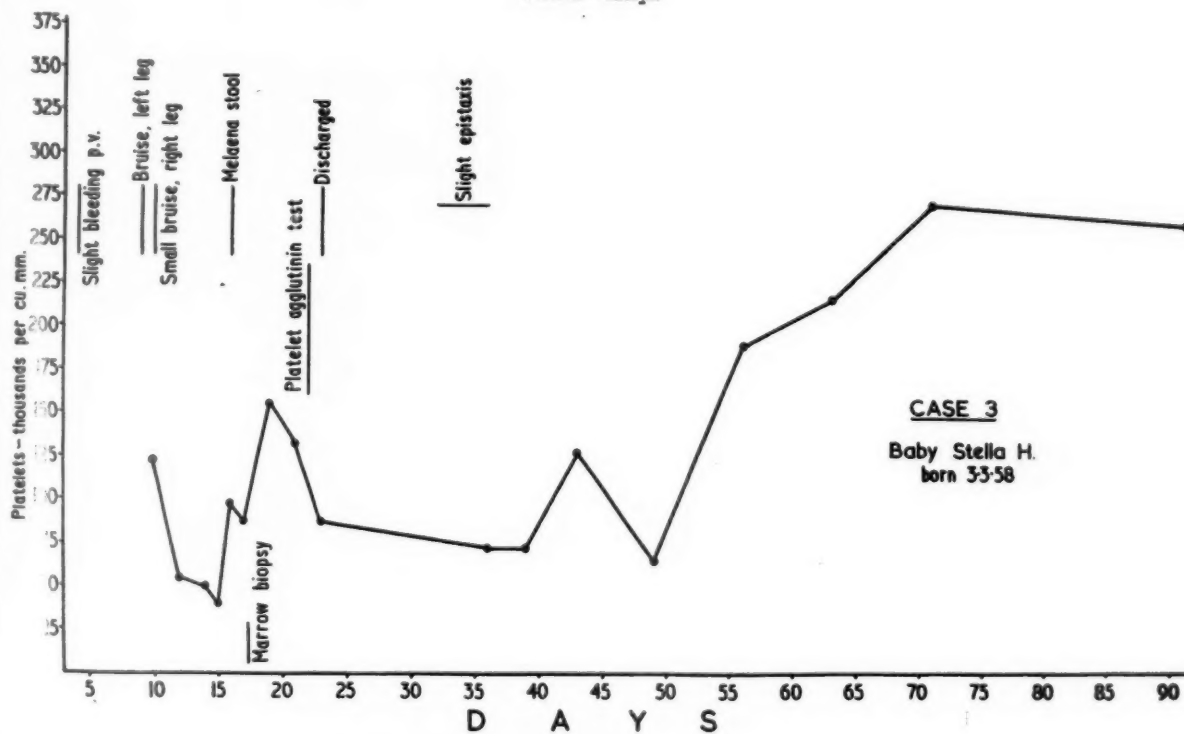


FIG. 9.—Case 3.

day after birth the platelet count was 124,000/c.mm., falling to 39,000/c.mm. during the succeeding five days. On the sixteenth day the child passed a melaena stool which soon cleared. No purpura was seen. A marrow examination carried out on the seventeenth day when the platelet count was 89,000/c.mm. showed scanty megakaryocytes again of intermediate and lymphoid types with little platelet production. Platelet agglutinins against her own platelets and those of a normal compatible control were demonstrable in the infant's serum when tested on the twenty-second day of life but the maternal serum failed to agglutinate the child's platelets. These results were also confirmed in a subsequent test. The child was discharged aged 23 days and after some fluctuations in the platelet count, associated with mild epistaxis when it stood at 72,000/c.mm., there was a gradual return to normal and the child had no haemorrhagic manifestations. She made a spontaneous recovery, no cortisone therapy being given.

Case 4. (Fig. 10.) Stephen H. was a brother of the previous patient and was three and a half years older. They were the only children of the marriage. Eleven days after birth he had an epistaxis of three to four days'

duration and the platelet count was found to be 83,000/c.mm. It subsequently fell to 63,000/c.mm. and then rose quickly and spontaneously to a normal level, since when the boy has remained well. Tests carried out in April, 1958 showed a normal platelet count of 308,000/c.mm., and no platelet agglutinins were demonstrable in his serum against his own platelets or those of a normal compatible control. The mother's serum also failed to agglutinate his platelets. No marrow biopsy was performed in the thrombocytopenic period shortly after birth and it was felt that no useful information would accrue by doing this after three and a half years when the boy was normal.

The familial aspect of these last two cases is very interesting.

Table 1 sets out the significant findings in the four cases described.

Additional Significant Observations

A family history of a bleeding tendency was obtained only in Cases 3 and 4. In the six parents

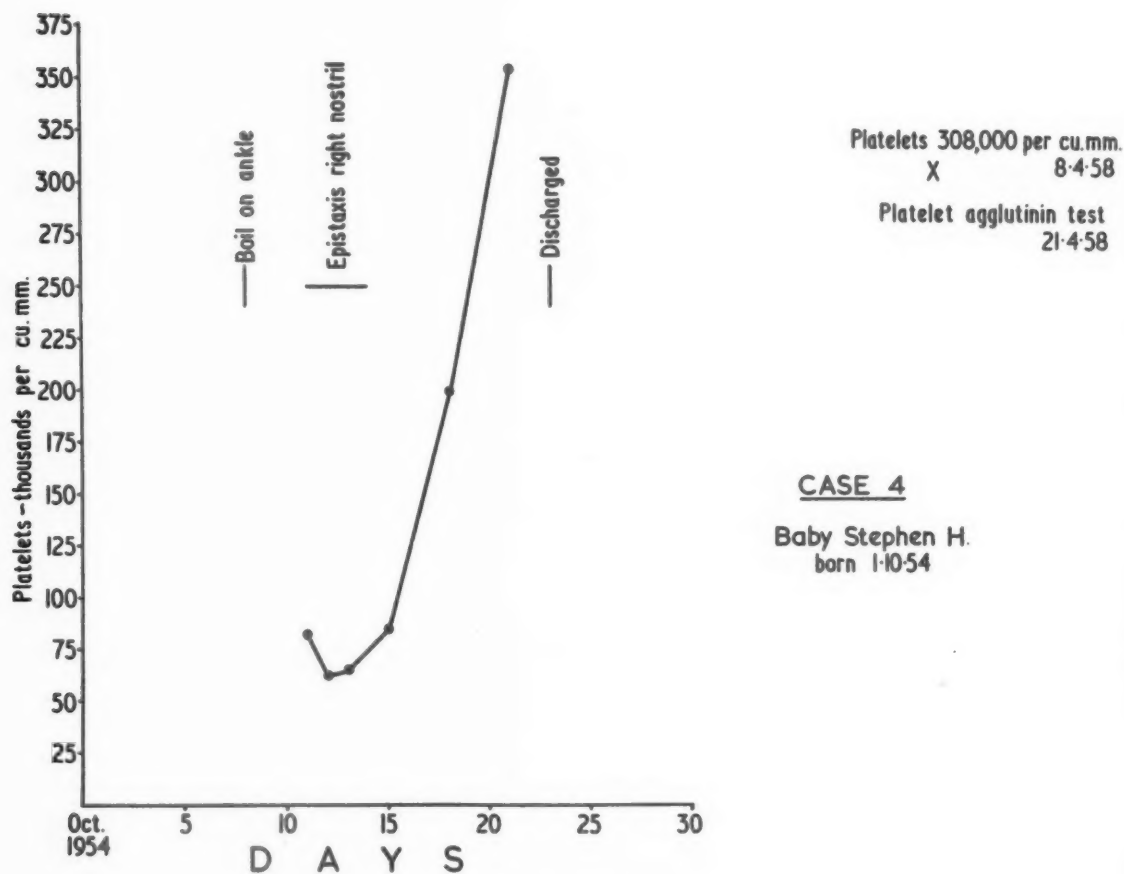


FIG. 10.—Case 4.

TABLE 1
CLINICAL DETAILS

Case	Age when Lesions Appeared	Site of Bleeding	First and Lowest Platelet Count (no./c.mm.)	Day of Lowest Count	Marrow Biopsy and Age	Platelet Agglutinations in Infant and Mother	Mother's First Platelet Count after Delivery (no./c.mm.) and Day
1 Paul B.	15 min.	Skin (purpura)	56,000 36,000	8	Megakaryocytes present but scanty; morphology as in I.T.P. (1 day) Megakaryocytes in normal numbers; morphology normal (26 days)	None	365,000 (1)
2 Andrea H.	6 hr.	Skin (purpura)	96,000 40,000	5	Megakaryocytes present but scanty; morphology as in I.T.P. (2 days)	None	286,000 (2)
3 Stella H. (sister of Case 4)	4, 9, 10, 16, 32 days	Vagina, skin (bruising), intestine, nose	124,000 39,000	15	Megakaryocytes present but scanty; morphology as in I.T.P. (17 days)	Present in infant against own platelets and those of normal control; mother—negative	658,000 (10)
4 Stephen H.	11 days	Nose	83,000 63,000	12	Not examined	Not tested at birth; none aged 3½ years	386,000 (12)

of the three families involved and in their relatives there was no suggestion of any haemorrhagic diathesis and platelet counts carried out on two or more occasions on each of the mothers were all within normal limits. No evidence of erythroblastosis foetalis was present clinically in any of the children shortly after birth. Anaemia was not a feature and the Coombs test in Cases 1, 2 and 3 was negative. All three mothers were Rhesus (D) positive, had negative Wassermann and Kahn reactions and were taking no drugs. Hypoprolthrombinaemia was excluded and in none of the infants was there any prolongation of coagulation time. The spleen was palpable only in Case 1.

The purpura in the first two cases disappeared within a week to 10 days as the platelet count rose following the administration of prednisolone. In Cases 3 and 4 (sister and brother), where haemorrhage involved other sites, recovery was spontaneous and also rapid. The marrow biopsies were obtained by aspiration from the tibia. The platelets were counted by the Lempert technique, and platelet agglutinins were tested against suspensions of platelets in both saline and albumen.

Discussion

The four cases recorded were the offspring of apparently healthy non-thrombocytopenic mothers (Group II in Robson and Walker's original classification). Even allowing for the fact that a

woman with idiopathic thrombocytopenic purpura (I.T.P.) may remit and be symptom-free during pregnancy, there was nothing to suggest this possibility in any of these mothers.

A marked reduction in megakaryocytes was a common feature in all three marrow examinations made during the early thrombocytopenic stage and this was unassociated with any general hypoplasia. This congenital hypoplasia of megakaryocytes accompanied by the morphological features already described suggests that the term 'congenital hypoplastic thrombocytopenia' may reflect the true nature of the condition and be a real entity (Hauser, 1948; Landolt, 1948). It is of some significance that Case 1 did in fact have other congenital lesions and that megakaryocytes appeared in normal numbers coincident with recovery. The familial incidence in Cases 3 and 4 is also compatible with a congenital aetiology, although in the first of these the finding of a platelet auto-antibody suggests some immune mechanism, as is often seen in chronic I.T.P. In the latter condition, megakaryocytes are characteristically plentiful in the marrow, and their paucity must be a strong point against this diagnosis. However, in two reported cases (Whitney and Barritt, 1942; Finn, 1944) of neonatal purpura occurring in infants of mothers with I.T.P., presumed but not proved to be due to an immune mechanism, the infant's marrow was found to be deficient in megakaryocytes at autopsy. There was

no suspicion of I.T.P. in the history of the mother of Case 3; she was also the mother of Case 4 and in each pregnancy her platelet count was normal. In both infants the somewhat late onset of symptoms (the fourth and eleventh day after birth respectively) also suggests that the cause was not related directly to the mother. It must be admitted that the serum of the elder child in this family (Case 4) was not tested for platelet antibodies at or shortly after birth. There was only a negative result at 3½ years of age, long after the thrombocytopenia had subsided, and this must be regarded as inconclusive. It is possible that these two children could be instances *de novo* of familial idiopathic thrombocytopenic purpura, although the marrow finding in the younger child is against this, and it is very unusual for this disease to manifest itself at such an early age.

Most cases of congenital hypoplastic thrombocytopenia recover rapidly and even spontaneously, although the administration of prednisolone in Cases 1 and 2 appeared to result in a rapid rise in the platelet count. Even in Case 3, where the megakaryocytic hypoplasia was associated with the demonstrable presence of a platelet antibody, recovery was rapid and unaided. The degree of megakaryocytic hypoplasia is probably an important factor in recovery since in the virtually complete amegakaryocytic types described by Greenwald and Sherman (1929), Bell, Mold, Oliver and Shaw (1956) and Emery, Gordon, Rendle-Short, Varadi and Warrack (1957), the outcome was fatal, there being no response to cortisone or splenectomy where this was tried, and there were other congenital malformations. In spite of the good prognosis in congenital thrombocytopenic purpura, provided the infant has survived the trauma of birth and provided the condition is not secondary to some infection, there is always the remote risk of the serious complication of intracranial haemorrhage, particularly when the platelet count is at a very low level and showing no tendency to rise. It is this hazard which makes treatment important. The chances of therapeutic success with either cortisone or splenectomy will depend ultimately on the degree of megakaryocytic

hypoplasia and should be tried in this order. If megakaryocytes are completely lacking no beneficial effect can be anticipated and splenectomy is contra-indicated.

Summary

Four babies with congenital thrombocytopenic purpura, whose mothers were apparently normal, have been reported. No agglutination was demonstrable between the sera of these mothers and the platelets of their babies. A platelet agglutinin was found in one infant. The marrow findings in three of the cases pointed to a congenital hypoplasia of the megakaryocytes, and in one instance a return to normal numbers and morphology concurrent with recovery was noted.

We wish to thank Dr. C. F. Harris and Dr. A. W. Franklin of the Paediatric Department of St. Bartholomew's Hospital, London, for permission to record these cases which were under their care, and we are also indebted to Miss B. Kirk for technical assistance in the haematological investigations.

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NEUROFIBROMATOSIS (VON RECKLINGHAUSEN'S DISEASE) OF THE VERTEBRAL COLUMN

BY

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(RECEIVED FOR PUBLICATION JUNE 1, 1959)

Although the occurrence of bone changes in von Recklinghausen's disease is uncommon, the incidence is difficult to determine, as mild cases are less likely to seek advice, particularly if the disease is already in the family. Holt and Wright (1948) thought it was greater than a previously estimated figure of 7%.

Of the bony deformities, scoliosis appears to be the commonest. Weiss (1921) described 15 cases of neurofibromatosis, all of whom had scoliosis. Brooks and Lehman (1924) studied seven cases with bone changes and found that all had scoliosis. They suggested that the lesion began with a neurofibroma of the periosteal nerve, and that this set up a reaction in the vertebra with bone destruction and regeneration. If actively bone-forming periosteum covers the tumour, a thin shell of bone forms over it and gives a cystic appearance. Weber (1930) described further cases and discussed various aspects of neurofibromatosis. Hagelstam (1946) reviewed the literature and collected 37 cases with deformity of the spine: two were in the cervical region, 20 in the upper and mid-dorsal regions and 15 in the dorsolumbar spines. Holt and Wright (1948) reviewed 127 cases of neurofibromatosis of which 29% showed skeletal involvement. The bone lesions consisted of erosive defects, scoliosis, growth disorders, bowing and pseudoarthrosis of the lower leg, intraosseous cystic lesions and associated anomalies. McCarroll (1950) found 19 cases of scoliosis in 43 cases with bone involvement.

Below are case reports of five children with neurofibromatosis of the spine.

Case Reports

Case 1. This girl was first seen at the age of 16 months on account of a 'bump in the back' which had been noticed from the age of 3 months. She was able to say several words with meaning and had learnt to sit without support at 10 months. She was unable to walk.

Her father, who was the youngest of 17 children, and

his father had von Recklinghausen's disease, but as far as we could tell the father's siblings were unaffected. We did not, however, examine them. Our patient was one of two children, both of whom had the disease.

On examination the girl presented the typical appearance of von Recklinghausen's disease with involvement of the vertebrae (Figs. 1 and 2). There were large pigmented and nodular areas in the groins (Fig. 3) and a severe kyphosis of the upper lumbar spine with chest deformity. Radiographs showed upper lumbar scoliosis with increased density and translucent areas in the anterior and posterior surfaces of the vertebrae (Fig. 4). There was considerable widening of the neural canal, suggesting the presence of a tumour mass. There was a spastic paraplegia with exaggerated tendon jerks, bilateral ankle clonus and a bilateral extensor plantar response. The neurosurgeon was not prepared to operate.

The girl subsequently put words together into sentences at 2 years and walked without help at 2 years and 3 months. At the age of 5 years she developed a headache, mainly occipital, and ataxia. She became drowsy and could no longer walk. On examination bilateral papilloedema was found, and a diagnosis of intracranial neurofibroma was made. She died at home.



FIG. 1.—Case 1, aged 16 months.



FIG. 2.—Case 1, aged 4 years.



FIG. 3.—Case 1, showing pigmented and nodular areas in groins.



FIG. 5.—Case 2.



FIG. 4.—Case 1.

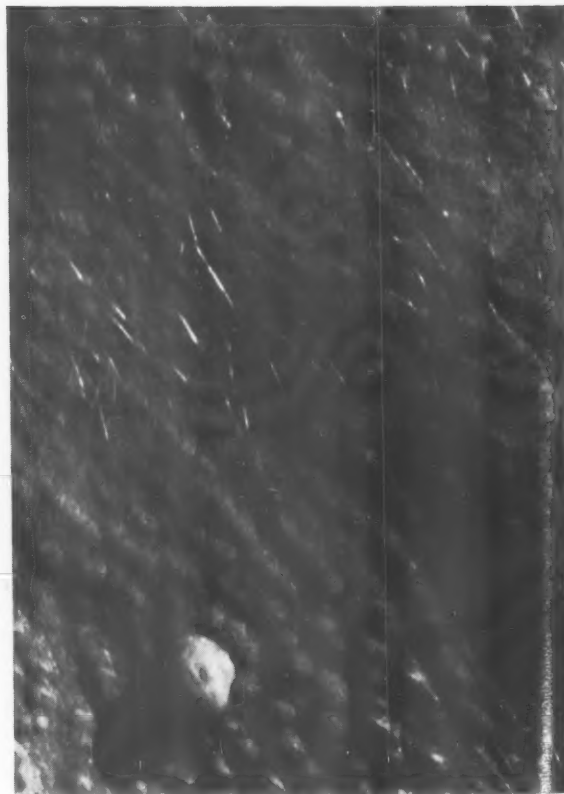


FIG. 6.—Case 2, close-up photograph of affected skin.

Case 2. This girl was under the care of an orthopaedic surgeon from the age of 6 months on account of dorsolumbar kyphosis. She was referred to a paediatrician at the age of 12 years because of cyanosis and dyspnoea on exertion. She had been brought up in a children's home from the age of 6 months having been neglected by the parents. The family history was unknown.

On examination at the age of 12 years there was a severe kyphosis maximal in the lower thoracic region (Fig. 5). There was widespread brown discolouration of the skin involving the lower half of the trunk, buttocks and part of the thighs. The skin in these areas was raised and pedunculated (Fig. 6). No other abnormal physical signs were found.

A radiograph of the vertebrae showed exaggerated pedicles (Fig. 7) and that of the left femur showed patchy calcification and cortical destruction (Fig. 8). A chest

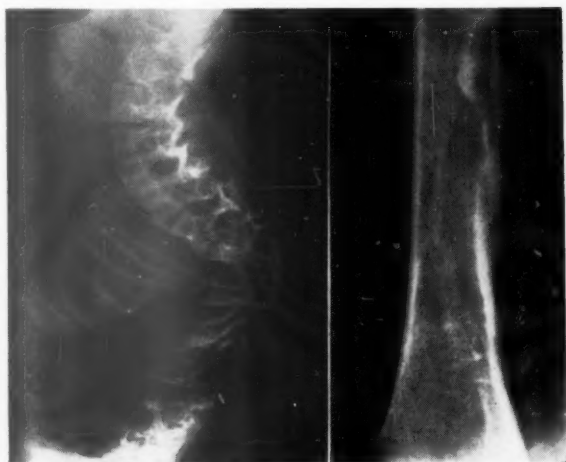


FIG. 7.

FIGS. 7 AND 8.—Case 2.

FIG. 8.

radiograph was normal and it was concluded that the respiratory symptoms were due to thoracic deformity. Skin biopsy confirmed the diagnosis of neurofibromatosis.

Case 3. (Figs. 9-11.) Swellings of the neck were noticed in this boy at 11 months. At the age of 14 months he was seen at the Leeds General Infirmary. There was a bilateral cervical adenitis with mottling of the skin. A radiograph showed collapse of the body of the fourth cervical vertebra. The tuberculin test was negative. Biopsy of the gland mass gave the appearance of a neurofibroma.

He was immobilized on a plaster of paris bed with headpiece from 2 years 2 months to 5 years 10 months, by which time the neck was grossly swollen by a nodular mass which in places infiltrated and reddened the skin. The area was generally freckled and pigmented and on the trunk there were café-au-lait patches. Radio-

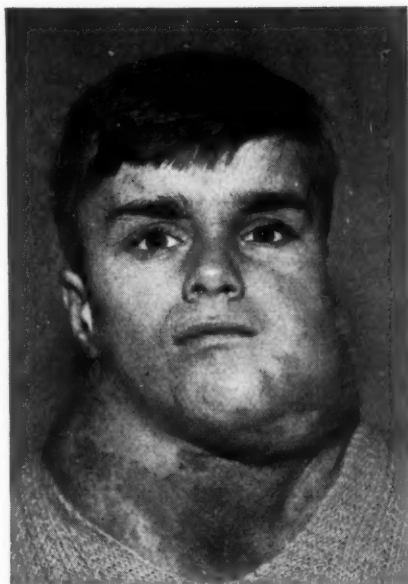


FIG. 9.—Case 3.



FIG. 10.—Case 3.

logically the condition of the neck was remarkable in that between the trachea and vertebral column there was a mass which had not pushed the trachea forward but had occupied a concavity of the cervical kyphosis as if it were responsible for the condition of the latter (Fig. 11). There had, however, been no specific change in the bones of the cervical vertebrae. An attempt was made to



FIG. 11.—Case 3.



FIG. 12.—Case 4, aged 6 years.

excise the mass at the age of 6 years 1 month but this was unsuccessful. The boy subsequently attended a school for physically handicapped children.

At the age of 15 years his height was $48\frac{1}{2}$ in. (1·21 m.) and his weight 48 lb. (21·8 kg.). He could walk fairly well but did not run. His appetite was good and he went to camp with the scouts.

FAMILY HISTORY. The mother felt on her face and body numerous painless nodules resembling neurofibromata. She remembered that they had appeared after an attack of 'erysipelas' at the age of 16.

Case 4. (Figs. 12-14.) Light brown spots were noticed on the trunk and thighs of this child between the ages of 1 and 3 years. They became more numerous and at the age of 6 years it was noticed that the back was curved.

On examination there were many café-au-lait macules up to the size of 3 cm., mainly on the trunk. There was a mid-dorsal scoliosis with convexity to the right. This could be passively but not actively reduced.

There was a gradual increase in the deformity in spite of orthopaedic treatment.

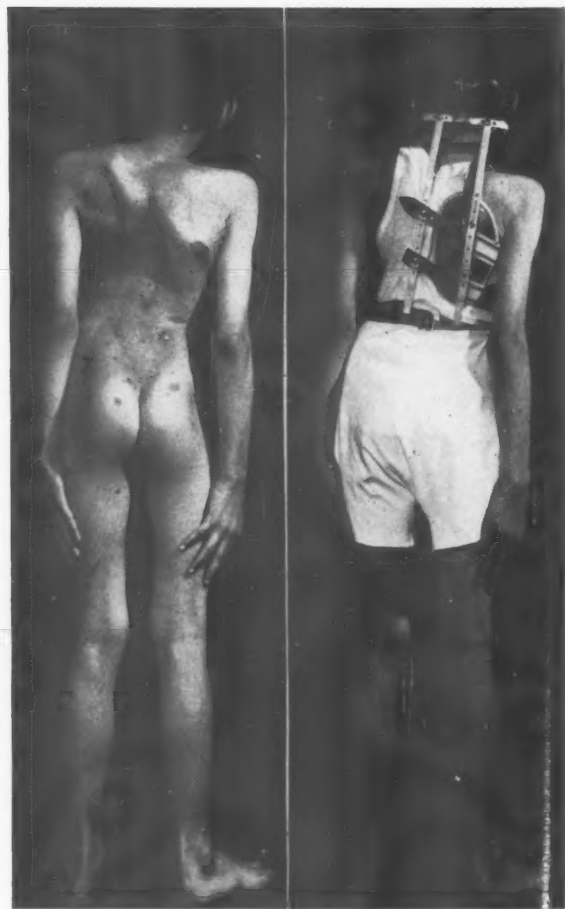


FIG. 13.—Case 4.



FIG. 14.—Case 4.

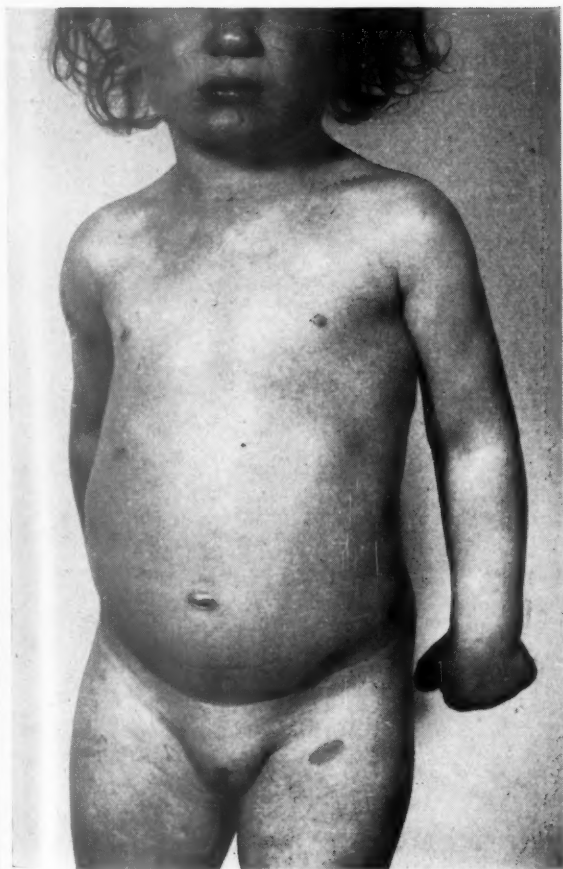


FIG. 15.—Case 5, aged 16 months.



FIG. 16.—Case 5, aged 2 years.



FIG. 17.—Case 5.

FAMILY HISTORY. The father had had brown spots, as had a paternal uncle and the paternal uncle's only daughter.

Case 5. A lump was noticed on the left side of the chest in the region of the nipple when the child was 16 months old (Fig. 15). When she was 2 years old a lump was noticed on the right side of the chest posteriorly (Fig. 16).

Examination at the age of 2 years showed that there was a scoliosis with the upper convexity to the left, the lower convexity to the right (Fig. 17). This largely disappeared when the child was lifted up. Over the trunk several café-au-lait patches were seen ranging from the size of a florin to a pea. No other skeletal deformity was noticed.

There was a gradual increase of the deformity in spite of physiotherapy.

FAMILY HISTORY. The mother was alleged to have been born with, or at all events to have developed shortly after birth, many coloured patches like those on the child. After the patient's birth soft lumps had appeared on her body, too.

Discussion

The changes in the vertebral column are of grave significance. Apart from a tendency to undergo malignant change, the lesions are progressive over

at least several years, reducing the patient to a cripple.

The diagnosis of neurofibromatosis may not be obvious if the skin lesions are minimal. In infancy there may be only one or two café-au-lait spots and several years may elapse before they become more numerous and prominent. While large subcutaneous masses are relatively frequent in infancy, the small polyp so characteristic in the adult is usually absent. The mother of Case 3 remembered that her nodules appeared at the age of 16 following an attack of erysipelas. The mother of Case 5 noticed the 'soft lumps' on her body after the birth of the patient.

In view of the grave prognosis, the diagnosis of neurofibromatosis should be considered in any case of unexplained scoliosis.

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TERATOMA OF THE NECK

REPORT OF TWO CASES AND REVIEW OF THE LITERATURE

BY

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Several difficulties were experienced in the diagnosis and management of the two cases which we are reporting. This was due to a lack of detailed knowledge of these tumours, which in turn was due to the absence in the literature of any adequate description of them and especially of their clinical features and treatment; this despite the three reviews which have so far been published (Saphir, 1929; Pusch and Nelson, 1935; Bale, 1950).

It is the object of this paper, therefore, to present a description, gleaned from reviewing the literature and from our own experience, of these tumours, their clinical manifestations and management. The

Definition

Teratomas of the neck are benign cystic, semi-cystic or solid tumours derived from the three germ layers. They are most commonly present in the foetus *in utero*, are sometimes associated with hydramnios and occasionally cause obstruction to labour. The infant may be full-term or premature; it may be stillborn, but is frequently alive at birth. The tumours often cause interference with respiration or swallowing at birth. Sometimes the tumours only become manifest later in infancy or childhood and rarely they may appear in adult life, in which case they are usually malignant.

TABLE 1
SUMMARY OF FINDINGS REVIEWED AND REPORTED BY SAPHIR AND BALE

Author	Sex			Thyroid Tissue			Brain Tissue			Thyroid Gland			'Displacement' of Thyroid Gland				Hydramnios			Operation performed			Thyroid Arteries Entering Tumour		
	M.	F.	No Ref.	Yes	No	No Ref.	Yes	No	No Ref.	Present	Absent	No Ref.	Yes	No	Doubtful	No Ref.	Yes	No	No Ref.	Yes	No	No Ref.	Definite	Doubtful	No Ref.
Saphir (1929): 29 cases reviewed; 1 case reported	10	13	7	15	11	4	24	0	6	19	4	7	17	0	6	7	4	12	14	17	13	0	2	3	25
Bale (1950): 26 cases reviewed; 4 cases reported	10	9	11	7	18	5	23	2	5	Not mentioned			19	1	2	8	9	8	13	13	17	0	3	0	27

two case reports illustrate the problems which can arise in dealing with these cases and add to the literature, which is not large.

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The tumours, which appear in the newborn infant and cause interference with respiration and swallowing, present as an urgent matter for diagnosis and treatment. This should not be a difficult problem, as will be shown, and the mortality from excision of the tumour is low provided that surgery

SUMMARY OF CASES

No.	Author and Year	Age	Sex	Race	Thyroid Tissue	Brain and Gland
1	Marescot (1945)	15 yr.	N.R.	N.R.	'Follicles with colloid'	N.R.
2	Lantuéjoul and Truffert (1946)	Birth	F.	N.R.	Yes	N.R. in; tumor of gland
3	Hellmuth (1950)	Birth	M.	N.R.	N.R.	Yes
4	Pozzi (1950)	Birth	M.	N.R.	Yes; near capsule	Yes in; tumor of gland
5	White and Gosselin (1952)	Birth	M.	White	Yes; near capsule also	Yes
6	McGoan (1952) Case 1	Birth	F.	Negress	N.R.	Yes gland
7	Case 2	Birth 34 wk prem.	M.	Negro	N.R.	Yes if indistinct
8	Case 3	? 8 mth.	M.	Negro	'Gland structures in capsule'	Yes
9	Case 4	Birth	M.	N.R.	N.R.	Yes
10	Salviati and Savegnago (1952)	Birth	N.R.	N.R.	N.R.	Yes lobe seen
11	Perkins and Pautler, (1953)	Birth	F.	N.R.	Yes; in capsule also	Yes right lobe
12	Otken (1953)	Birth	M.	N.R.	Yes; beneath capsule	Yes to superior
13	Hinds, Seybold and Walker (1954)	Birth	N.R.	Negro	Yes	Yes to thyroid
14	Buckwalter and Layton (1954)	28 yr.	F.	N.R.	N.R.	Yes right lobe left
15	Kresse (1954)	Birth	M.	N.R.	N.R.	N.R.
16	Cavallero (1954)	24 yr.	M.	N.R.	Yes	Yes
17	Malaspina and Somaglino (1955)	Birth	M.	N.R.	N.R.	N.R. in position
18	Kaminek and Tomik (1957)	Birth 27 wk. prem.	F.	N.R.	N.R.	Yes absent; to right
19	Salas, Esparza, Angulo and Castañeda (1957)	Birth	F.	N.R.	N.R.	Yes
20	Thomas (1957)	Birth	F.	W. African Negress	N.R.	Yes
21	Silberman and Mendelson (1960) Case 1	Birth	M.	White	Yes	No not seen
22	Case 2	Birth	F.	White	Yes	Yes thyroid gland

is undertaken before deterioration in the condition of the infant has occurred.

Incidence

Saphir (1929) reviewed 29 cases and added one of his own. Bale (1950) reviewed 26 additional cases and added four of his own (Table 1). We have collected 20 previously unreviewed cases (Table 2) which include a case (Marescot, 1945) mentioned but not included in Bale's review (the second case in Marescot's paper is not included because of lack of histological confirmation of the nature of the tumour), a case omitted by Bale (Lantuéjoul and Truffert, 1946) and 18 other cases. There is therefore a total of 82 cases in the literature

to date, including the two reported in this paper.

These tumours are not quite as rare as might be thought when compared with the number of reported cases of teratoma in other sites, e.g. retroperitoneal teratoma (59 cases up to 1949) or mediastinal teratoma (245 cases up to 1945), but these included dermoids and epidermoids as well as teratomas. (These figures are quoted by Gross, 1953.)

Case Reports

Case 1. A full-term white male infant was admitted to Hope Hospital, Salford as an emergency on April 25, 1957, having been born at home three hours earlier. The mother, aged 28 years, had had two previous normal deliveries. Pregnancy in this case was normal; labour

CASES REVIEWED

Brain	Hydramnios	Signs and Symptoms	Treatment and Results
N.R.	N.R.	N.R.	Operation at 36 yr.; no reference to result
N.R. in; tumour in of gland	Yes	Dyspnoea and apnoea	Operation eighth day; no anaesthetic; died post-operatively
Yes	N.R.	Stridor; cyanosis	Operation at 3 days; post-operative jaundice; well at 2 mth.
Yes in; tumour in of gland	N.R.	Asphyxia	Died shortly after birth
Yes	No	Vomiting; dyspnoea	Excision at 3 days; well at 7 mth.
Yes gland	N.R.	Fever, hoarseness and anorexia at 6 mth.; bronchitis and pneumonia	Treatment of pneumonia died 2 wk. later
Yes self indistinct	N.R.	Cyanosis; weak respiration	Died 1 hr. after birth
Yes	N.R.	Difficult respiration and respiratory infection at 8 mth.	Operation and post-operative tracheostomy; well 3 wk. later
Yes	N.R.	Vomiting; respiratory distress	Caecostomy for imperforate anus; died 2 wk. later
Yes lobe seen	N.R.	Asphyxia; feeding difficulties at birth, then asymptomatic	Operation (local anaesthetic) at 40th day; temporary post-operative paralysis of vocal cord; well thereafter
Yes right lobe	No	None	Excision 6th day; post-operative temporary paralysis of vocal cord; well at 4½ mth.
Yes to superior pole	No	Increase in size of tumour	Enucleation at 3 wk.; well at 6 wk.
Yes to thyroid	N.R.	None	Excision at 3 yr.; uneventful recovery
Yes right lobe and left	N.R.	Ache; increase in size of thyroid	Total thyroidectomy and radical neck dissection; post-operative radiotherapy and ¹³¹ I treatment; died of metastases 1½ yr. later
N.R.	No	Apnoea	Died shortly after birth
Yes	N.R.	N.R.	Excision at 46 yr.
N.R. in position of	N.R.	None	Operation at 7½ mth.; no reference to result
Yes absent; tumour to right lobe	Yes	Apnoea and cyanosis	Died ½ hr. after birth
Yes	N.R.	Cyanosis at birth; dyspnoea; respiratory infection and atelectasis at 6½ wk.	Tracheostomy and cardiac massage at 6½ wks.; died
Yes	N.R.	Slight stridor at 4 mth.	Enucleation-excision at 4 mth.; well 1 wk. later
No not seen	No	Dyspnoea and cyanosis at birth	Excision 6 hr. after birth; well at 2 mth.
Yes thyroid gland	No	Rapid respiration; retained secretions; 'moist' chest	Excision at 4 days; died 2 days later; bronchopneumonia

lasted approximately 10 hours and was reported by the midwife in attendance as having been uncomplicated. Both parents were healthy and there were no known familial diseases.

The infant, who was well developed, was extremely ill with very rapid respiration which was 'grunting' in character; there was deep cyanosis and marked rib recession; the heart and lungs were normal. The rest of the general examination was negative.

EXAMINATION OF NECK (Figs. 1 and 2). There was a spherical tumour about 7.5 cm. in diameter situated on the left side of the neck extending from the parotid region above to the clavicle below and from over the midline medially well into the posterior triangle. It was hard, without any cystic areas, and its surface was boggy. The skin over the surface of the tumour

was freely mobile. On its deep surface the tumour appeared to have some attachment in the vicinity of the larynx and thyroid gland but was only loosely attached elsewhere so that the entire tumour was mobile in all directions and hung down over the anterior chest wall because of its weight. The left pinna was displaced upwards and the left half of the body of the mandible appeared to be displaced upwards. The larynx and trachea were obscured by the medial border of the tumour.

The infant was placed in an incubator and given continuous oxygen with some improvement but soon became again deeply cyanosed and limp and appeared to be moribund. Coramine 0.5 ml. and eucortone 0.5 ml. were given intramuscularly and oxygen was given by face mask with marked improvement, but the respiration nevertheless remained difficult and cyanosis persisted.



FIGS. 1 and 2.—Case 1.
Lateral views of tumour.

FIG. 1.

FIG. 2.

A radiograph of the neck (Fig. 3) showed the presence of a soft tissue tumour on the left side of the neck; there was no calcification of the tumour. The trachea was compressed antero-posteriorly; the left half of the mandible showed an absence of the normal angle between body and ramus and these two formed a straight line from the symphysis menti to the base of the skull. The chest was normal.

Tracheostomy was not possible because the tumour overlapped the midline. Excision of the tumour appeared to offer the only possible chance of success. A tentative pre-operative diagnosis of congenital malignant tumour was made.

OPERATION. This was undertaken about three hours after admission under general anaesthesia with endotracheal intubation. A curved skin incision was made, medial and lateral skin flaps were raised and the tumour

was dissected out of its bed with ease because of the well defined capsule and the lack of attachment except in the vicinity of the larynx and thyroid gland, where careful dissection was necessary. It was not possible to ascertain whether the blood supply of the tumour originated in the thyroid arteries or not. No attempt was made to identify the thyroid gland. Haemorrhage during the operation was minimal. The wound was closed with interrupted skin sutures and a Penrose drain was brought out through the wound. The operation was well tolerated.

The drain was removed after 48 hours and the skin sutures on the eighth post-operative day. There were no respiratory difficulties except for stridor, which appeared if the infant was disturbed. Cyanosis did not recur.

The infant was discharged after three and a half weeks

FIG. 3.—Case 1. Lateral radiograph showing soft tissue shadow, compression of trachea and absence of angle of left mandible.



FIG. 3.



FIG. 4.

FIG. 4.—Case 1. Post-operative view of neck.

in hospital (Fig. 4), having gained weight progressively. The wound was well healed, breast feeds were being taken normally and there were no respiratory difficulties.

The infant was asymptomatic and healthy when seen at follow-up two months later.

APPEARANCE OF GROSS SPECIMEN. This was an almost spherical, solid tumour measuring $7.5 \times 6.5 \times 6.5$ cm.

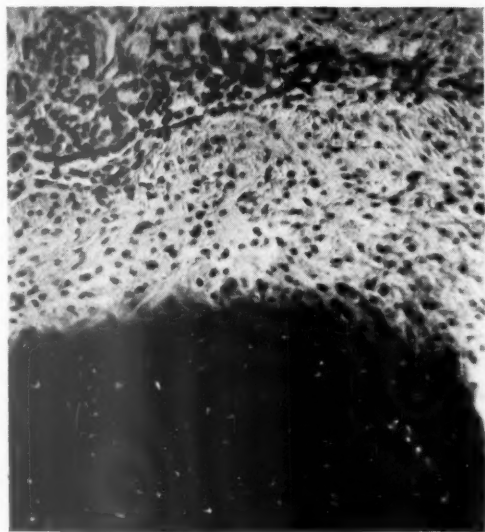


FIG. 5.—Case 1. Photomicrograph showing cartilage in its lower half.

It was greyish-white in colour and the surface was irregular and lobulated. The tumour was well encapsulated.

The cut surface was firm and fibrous with scattered areas of what appeared to be cartilage.

MICROSCOPICAL APPEARANCE (Figs. 5 and 6). Dr. G. J. Crawford (Hope Hospital) reported:

'The tumour is well circumscribed and in places has a thin fibrous capsule from which fibrous trabeculae run inwards. In several places compressed thyroid tissue is present in the capsule; groups of thyroid acini are also seen in the tumour, strands of epithelial cells and a small island of squamous cells. About half the tumour is composed of fairly cellular fibrous tissue, about one-third of cartilage and the remainder of small areas of myxoid tissue and fat. There is one small area of undifferentiated mesenchyme in which two mitoses were observed. In many of the sections there are scattered foci of haemopoiesis; some of these are associated with fat and thin-walled blood vessels as in bone marrow. The tumour is well supplied with blood vessels, mostly capillaries. No nerve tissue was found. All the tissues in the tumour are either found normally in this area or could be formed from the local mesenchyme. I consider that it is a malformation (hamartoma).'

The tumour was shown to the Children's Tumour Registry of the University of Manchester whose panel of pathologists kindly examined the sections. Their reports and comments are, with their kind permission, given below.



FIG. 6.—Case 1. Photomicrograph showing thyroid follicles.

Professor A. C. P. Campbell (University of Manchester):

'Either a teratoma or a mixed tumour of ectopic tracheo-bronchial anlage. I think it is more probably the latter; all the tissue elements present are compatible with a tracheal origin (explaining the squamous epithelium as metaplastic). It appears benign.'

Dr. Agnes R. Macgregor (Royal Hospital for Sick Children, Edinburgh):

'The tumour is composed of a mesoblastic tissue among which are many masses of cartilage. The mesoblastic tissue varies in character from a moderately cellular collagenous tissue to virtually undifferentiated mesenchyme, in which mitoses are numerous; there are also myxomatous areas. There are atrophied thyroid vesicles at the periphery and epithelial acini, probably of thyroid tissue, appear here and there in the substance of the tumour. No other varieties of tissue are identified.

Inference: It may be a teratoma, but as the epithelial elements appear to be thyroid tissue and all the other elements are mesoblastic, it seems to fit very well the description of the "mixed tumour of the thyroid" mentioned by Willis in *Pathology of Tumours*, 1948, p. 616. The less differentiated parts are histologically malignant.'

Dr. H. Marsden (Royal Manchester Children's Hospital):

'There is loose mesenchymal tissue with spindle cells and numerous islands of cartilage. In addition follicles lined by cuboidal epithelium and containing eosinophilic material are noted. The latter resemble thyroid follicles. The picture is that of a benign teratoid tumour.'

Dr. H. Russell (Christie Hospital, Manchester):

'A defined mass of anomalous mesenchyme in which well-formed cartilage is conspicuous. There appears to be a rim of thyroid tissue closely applied to its periphery. An anomaly of development of the branchial arches.'

R. A. Willis (Prof. Emeritus, University of Leeds):

'A most unusual tumour, composed of moderately cellular vascular mesenchyme with many areas of chondrification, in which some thyroid vesicles and tortuous epithelial strands are incorporated. Thyroid tissue is also present around its well-defined margin. The two possibilities are (I) teratoma, and (II) a chondromatous hamartoma of the thyroid; because of the incorporation of thyroid tissue, I incline to (II). But further sections should be made, in search of other teratomatous tissues. In my opinion the growth is probably benign.'

Even though no uniformity of opinion has been expressed by the panel of pathologists, many of them classified the tumour as a teratoma. For this reason and also because of the extremely close resemblance, both clinically and pathologically, of this tumour to the cases previously reported in the literature as teratoma of the neck, it has been thought quite justifiable to classify it as such.

Case 2. A full-term white female infant was admitted to Memorial Hospital, New York, on June 28, 1949, having been born elsewhere 21 hours previously. The mother, a 28-year-old primipara, had persistent nausea throughout the pregnancy which was otherwise uneventful. Labour lasted 20 hours and the infant was delivered by mid-forceps because of a persistent occipito-posterior position. The weight at birth was 7 lb. 4 oz. The infant had required suction of the mouth and pharynx at birth because of an accumulation of secretions; she had vomited fluids given to her by mouth.

The infant was well developed and was in mild distress from accumulated secretions in the pharynx. Respiration was 44 per minute, heart rate 144 per minute and temperature 99° F. There were numerous rhonchi in the left lung anteriorly. The rest of the general examination did not reveal any other significant findings.

EXAMINATION OF NECK (Figs. 7 and 8). There was a firm, rounded, mobile mass about 14 cm. in diameter situated in the left side of the neck. It extended from the midline of the neck into the posterior triangle; superiorly it extended onto the face and reached the level of the external auditory meatus. Inferiorly, it extended



FIG. 7.—Case 2.
Anterior view of tumour.



FIG. 8.—Case 2.
Lateral view of tumour.

to the root of the neck. The head was displaced to the right. There were a few dilated vessels on the surface of the mass. The anterior part of the mass appeared to be cystic but the rest of the tumour was solid.

INVESTIGATIONS. A blood count and chemical and microscopical examinations of the urine were normal.

A chest radiograph was normal.

A radiograph of the neck (Fig. 9) showed that the tumour contained multiple areas of calcification; the trachea, larynx and oesophagus were normal.

The tumour was aspirated and found to be multilocular; 50 ml. of sero-sanguinous fluid was obtained.

The infant took glucose feeds but vomited frequently; her weight dropped to 6 lb. 6 oz. There were periods of

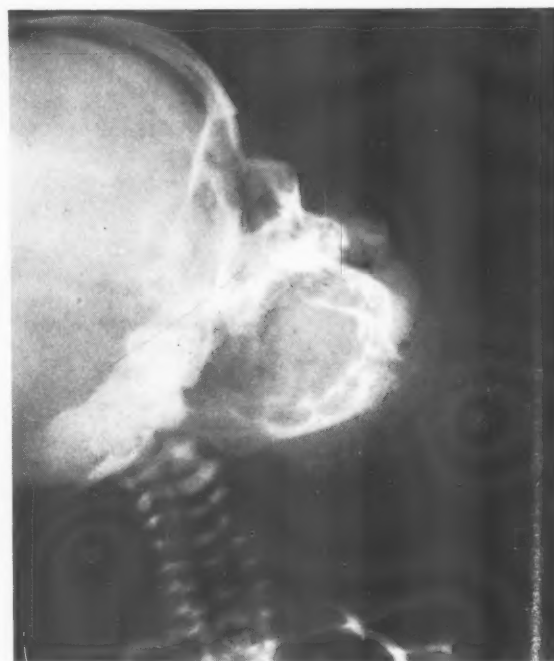


FIG. 9.—Case 2. Lateral radiograph showing calcification in tumour.

cyanosis and difficulty with respiration, which required frequent suctioning. It was decided that an emergency operation would be necessary. The pre-operative diagnosis was between cystic hygroma, branchial cleft cyst and dermoid cyst.

OPERATION (JULY 1, 1949). Without anaesthesia, an H-shaped incision was made and the tumour was dissected from its bed and removed with its capsule intact. The origin of the blood supply of the tumour was not accurately identified and the thyroid gland was not visualized. The skin was approximated with fine nylon sutures and a Penrose drain was brought out from the wound. The operation was well tolerated.

The infant was placed in a steam tent with oxygen and was given injections of penicillin. She was given tube feeds because she was unable to take oral feeds, but some regurgitation occurred. Thirty-six hours post-operatively her temperature rose and she developed massive consolidation (or collapse) of the left lung and broncho-pneumonia of the right lung. Her condition deteriorated rapidly and she died on the second post-operative day.

AUTOPSY (JULY 4, 1949). This showed that death was due to bilateral severe broncho-pneumonia with abscess formation; aspirated material was present in a few of the bronchi. The thyroid gland, which was grossly normal, was removed and found to be histologically normal.

projected a mass measuring $5.5 \times 5 \times 4$ cm. The lining of the cyst was grey to grey-tan in colour and contained a few yellow-grey plaques up to 3 mm. in diameter. The sectioned surface of the mass was made up of innumerable tiny thin-walled cysts measuring from 1-10 mm. in diameter. These cysts contained clear mucoid material. Scattered throughout the mass were areas of calcification up to 8 mm. in diameter.



FIG. 11.—Case 2. Cut surface of tumour.

MICROSCOPICAL APPEARANCE (Figs. 12-14). The tumour was found to be a benign teratoma which



FIG. 10.—Case 2. Operative specimen. Note excellent capsule.



FIG. 12.—Case 2. Photomicrograph showing choroid plexus.

APPEARANCE OF GROSS SPECIMEN (Figs. 10 and 11). A well-encapsulated, grey-tan rounded tumour measuring $7.5 \times 6.5 \times 5.5$ cm. was found on section to consist of a large cystic cavity containing bloody fluid into which

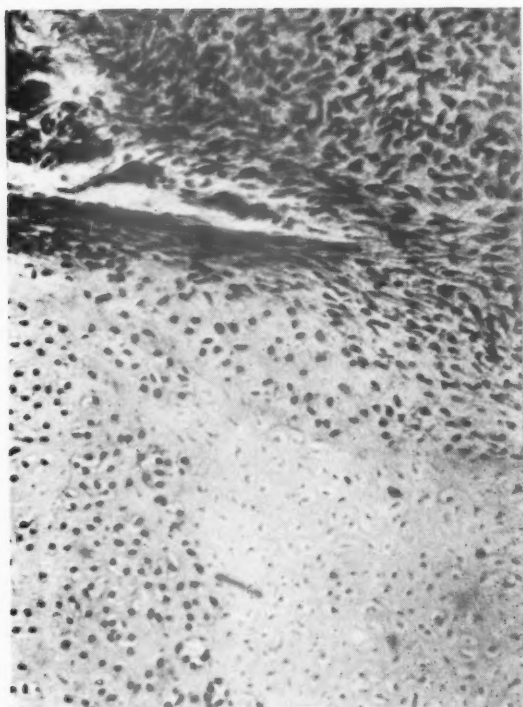


FIG. 13.—Case 2. Photomicrograph showing cartilage.

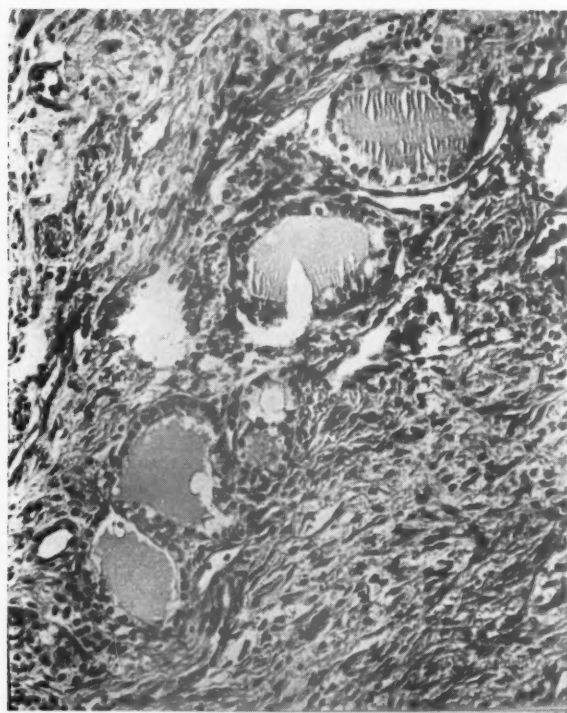


FIG. 14.—Case 2. Photomicrograph showing thyroid follicles.

contained cysts lined with squamous, cuboidal or columnar epithelium; other cysts contained papillary projections. Bronchial epithelium, smooth muscle, immature cartilage and embryonic connective tissue were identified. Thyroid follicles and brain tissue (nerve fibres, glia, choroid plexus) were also in evidence.

Discussion

Nomenclature. Attempts have been made in the past to define which tumours should be called teratoma of the thyroid gland and which should be called cervical teratoma.

Saphir (1929) stated that if the thyroid gland was absent the tumour was a thyroid teratoma, but that if the thyroid gland was present the tumour was a teratoma of the neck. These criteria, we think, are basically sound but require further elaboration and clarification.

Bale (1950) disagreed with Saphir's method of classifying the tumours and instead proposed a more complicated nomenclature, viz. (a) teratoma of the thyroid gland if the thyroid arteries supplied the tumour; (b) teratoma of the neck in the region of the thyroid gland if the tumour replaced all or part of the gland; and (c) teratoma of the neck, probably in the region of the thyroid gland, because of the general appearance of the tumour. This classification suffers from several objections. Firstly, the fact that the thyroid arteries supply the tumour cannot be accepted as evidence that the tumour has its origin in the thyroid gland; these arteries supply many structures other than the thyroid gland and a tumour supplied by them may have arisen from any one of these structures, e.g. parathyroids, larynx, soft tissues. Secondly, very few reports in the literature mention the blood supply of the tumour and hence are unclassifiable on Bale's criteria. Thirdly, in carrying out an emergency procedure for a cervical teratoma on a newborn infant, it would be extremely unwise to search for the thyroid arteries if they were not easily visible (this obviously does not apply to autopsy specimens). Finally, the creation of three categories of tumour, as proposed by Bale, appears cumbersome and unnecessary.

We propose that the tumour be referred to as a cervical teratoma unless it fulfills the following criteria, in which case it may be called a true teratoma of the thyroid gland. The teratoma is situated in the position of the thyroid gland and in addition (a) the thyroid gland is present and the tumour occupies a portion of it; or (b) the thyroid gland is only partially present, but the tumour is in direct continuity with it, the two forming one mass; or (c) the thyroid gland is completely absent and the tumour replaces the gland entirely.

When a teratoma is adjacent to, but not in direct continuity with, a thyroid gland which may be only partially present, then the tumour cannot be classified as a true teratoma of the thyroid gland because the tumour may well have arisen outside the gland and given rise to atrophy of the gland by pressure.

The presence or absence in the tumour of thyroid tissue is of no particular value in classification since by their very nature all teratomas are capable of producing a wide variety of tissues, and thyroid tissue is no exception.

Accordingly the following cases which have appeared since 1945 should be referred to as true thyroid teratomas: Cases 2, 4, 12, 14, 17 and 18 (see Table 2), possibly Cases 5 and 13 (see Table 2) and Bale's (1950) first three cases.

Age. The age distribution in 79 of the 82 cases reported to date in which age is mentioned is seen in Fig. 15.

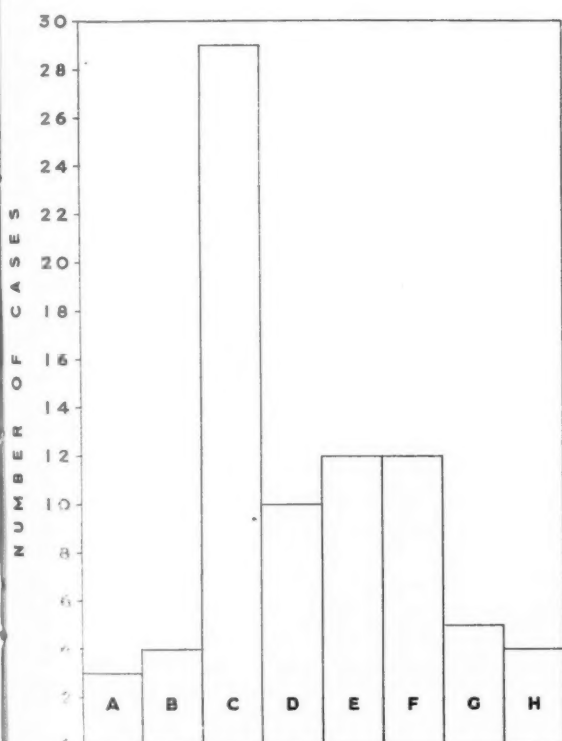


FIG. 15.—Age distribution of 79 cases.

- A = live premature infants
- B = stillborn premature infants
- C = live full-term infants
- D = stillborn full-term infants
- E = birth to 1 month
- F = 1 month to 1 year
- G = 1 year to 15 years
- H = adults

Neither Saphir's (1929) nor Bale's (1950) reviews state whether they refer to the date of appearance of the tumour or the age of the patient when first seen. Nevertheless, it can be presumed that most, if not all, of the cases up to 1 month old and many of those up to 1 year old had the tumour at birth. In those cases which we have collected we have taken care to utilize the age at appearance of the tumour and not the age of the patient when first seen.

In any case, it can be seen from Fig. 15 that the majority of tumours were present at birth although some do not appear to present until later. The tumour is rare after the age of 1 year.

Sex. The sex of the patient was mentioned in 61 cases out of 82 in the literature, of which 30 were females and 31 were males.

Race. Although most of the tumours have appeared in white patients, they have also been reported in Negroes (Saphir, 1929; McGoon, 1952; Hinds, Seybold and Walker, 1954; Thomas, 1957).

Histology. All varieties of tissue from the three germinal layers have been found in these tumours. Particular mention has been made in the past of brain tissue, which has been observed in 47 of 60 cases of Saphir's and Bale's and in 17 of our 22 cases, and also of thyroid tissue, which was present in 22 of Saphir's and Bale's 60 cases and in 11 of our 22 cases (see Tables 1 and 2).

The vast majority of tumours were benign on histological examination but, unfortunately, there has been no long-term follow-up on them. Four definite cases of malignancy have been reported to date. Three were mentioned by Bale (1950). The first was a 9-week-old infant, who died on the day of operation (Pupovac, 1896). The second was a 53-year-old woman, who died of metastatic pulmonary sarcoma from probable malignant proliferation of the teratoma (Lurje, 1908). The third was a 41-year-old female, who died one month post-operatively of widespread metastatic sarcoma, probably originating in the teratoma (Fritzsche, 1920). The fourth case was reported in 1954 by Buckwalter and Layton. Their patient was a 28-year-old female, who died of metastases 15 months after total thyroidectomy and radical neck dissection. The tumour had caused progressive enlargement of one lobe of the thyroid gland for a period of six months prior to surgery. On histological examination it was found to have contained immature neural tissue and muscle as well as cartilage, mesenchyme and gland structures.

Signs and Symptoms. The following remarks are based on a close study of all the cases reported since

1945 (see Table 2) and therefore include Bale's (1950) four cases.

The majority of tumours were oval in shape; an occasional one was spherical. In size, except for Cavallero's (1954) case, in which the tumour was the size of a nut, most of the tumours were between 5 cm. and 12 cm. in their longest axis. When compared with the antero-posterior diameter of a newborn infant's head, which is 10 cm. (approximately), it can be appreciated that these tumours are quite large.

Most of the tumours were situated on one or other side of the neck, usually extending up as far as the mastoid process and body of the mandible and often displacing the lobule of the ear upwards; many tumours reached the zygomatic arch. Posteriorly they usually reached the anterior border of trapezius and anteriorly they often crossed the midline for a short distance. The inferior border of the tumour was most frequently the clavicle but in two cases the tumour entered the mediastinum (Salas, Esparza, Angulo and Castañeda, 1957; Kaminek and Tomik, 1957). In four cases (Lantuéjoul and Truffert, 1946; McGoon's third case, 1952; Pozzi, 1950; Malaspina and Somaglino, 1955) the tumour was situated in the position of the normal thyroid gland and was mistaken for a congenital goitre. The tumour reported by Buckwalter and Layton (1954) was the only one which was palpated as a swelling in a lobe of the thyroid gland; but this tumour occurred in an adult aged 28 years who had a malignant teratoma.

The consistency of the tumour varied. It was cystic, or partly solid and partly cystic, or entirely solid. However, in most instances fluctuant cystic areas were palpable. An occasional case was transilluminated. The surface of the tumour was usually irregular, being described as lobulated, bosselated or loculated, and the borders of the tumour were usually well defined.

In only a few case reports was the mobility of the tumour mentioned. In these cases the tumour was usually quite mobile as was the skin on the surface of the tumour. A few reports mentioned that there were collateral veins on the surface of the tumour.

The cases which were not stillborn usually had acute symptoms at birth. These were cyanosis, dyspnoea, apnoea and stridor due to tracheal deviation and/or tracheal compression. In a few instances swallowing difficulties occurred. These symptoms often led to a fatal termination if early treatment was not undertaken (McGoon, 1952; Kaminek and Tomik, 1957). Occasionally, the infant was asymptomatic at birth and only several weeks or months later developed serious symptoms (McGoon, 1952; Salas *et al.*, 1957) and in a few

instances the tumour remained entirely asymptomatic (Otken, 1953; Hinds *et al.*, 1954).

The presence and degree of tracheal deviation and obstruction was often demonstrable radiologically. The radiograph also showed calcification of the tumour in a few cases, as occurred in our second case, in McGoon's (1952) fourth case and in Thomas's (1957) case.

Aspiration of the mass was performed in the case described by Lantuéjoul and Truffert (1946). They obtained opalescent fluid but were not able to empty the cyst of its contents, indicating its multilocular nature. Our second case was aspirated and sero-sanguinous fluid was obtained; aspiration also showed that the tumour was multilocular.

Effects of Tumour on Pregnancy and Labour. There have been two cases of hydramnios in the cases reported since 1945 (Lantuéjoul and Truffert, 1946; Kaminek and Tomik, 1957). Before 1945 13 cases had been reported (Table 1), making a total to date of 15 instances in 82 case reports (18%). This coincides well with the high incidence of hydramnios which is known to occur in cases of foetal malformation. Hydramnios is often associated with anomalies such as oesophageal atresia, in which the foetus is unable to swallow the liquor amnii. This is postulated as an aetiological factor in hydramnios (Eastman, 1956). It is possible that the oesophageal obstruction produced by a cervical or thyroid teratoma is in a similar manner responsible for the high incidence of hydramnios in these cases.

The size of the tumour may impede labour and may require the application of forceps (White and Gosselin, 1952; Kresse, 1954; our second case) or caesarean section (Salviati and Savegnago, 1952) or episiotomy (Perkins, Pautler and Winston-Salem, 1953). In the case reported by Salviati and Savegnago (1952) the tumour was stated to have been palpated in the abdomen and per vaginam.

Associated Congenital Anomalies. Two instances of associated congenital anomalies have appeared since 1945: 'chondro-dystrophia foetalis' was present in McGoon's (1952) second case and imperforate anus in his fourth case.

Differential Diagnosis. Some of the diagnoses, which have been considered by various authors pre-operatively, are cystic hygroma, congenital goitre, branchial cyst, lymphangioma, simple multilocular cyst, dermoid cyst, neuroblastoma, parotid tumour and carcinoma of the thyroid gland (in Buckwalter and Layton's case of malignant teratoma in an adult).

The chief tumours which require differentiation are cystic hygroma, congenital goitre and branchial cyst.

In age incidence, sex incidence, site, size and surface of the tumour, teratoma and cystic hygroma are similar. However, a cystic hygroma usually has a limpid consistency and poorly defined borders and is easily transilluminated (Gross, 1953); teratomas are often tense or solid in consistency, have well defined borders, are usually freely mobile and only occasionally can they be transilluminated. Radiography may demonstrate calcification in teratomas but not in hygromas. Finally, hygromas produce few symptoms, except when infected or very large, which is in direct contrast with the respiratory and feeding difficulties commonly seen with teratomas.

In those instances in which the teratoma occupies the position and has the shape of a thyroid gland it must be differentiated from a congenital goitre. However, since congenital goitres are rare outside endemic areas (McQuarrie, 1957), the problem is practically limited to these areas. Radiography of the neck may be of value in demonstrating the presence of calcification in a teratomatous tumour.

The following features of a branchial cyst serve to differentiate it from a teratoma: it is commonest in the third decade and presents as a smooth, globular swelling deep to the anterior border of the sternomastoid muscle, usually at its middle; on aspiration typically it yields a milky fluid containing cholesterol crystals (Aird, 1957).

Prognosis and Treatment. Forty-six patients of all those reported thus far (82) have undergone surgery, and seven died. Of the deaths, three occurred in patients with malignant tumours: one was an operative death, the second was an adult who died of metastases (both mentioned by Bale, 1950) and the third was also an adult who died of metastases (Buckwalter and Layton, 1954). Of the remaining four deaths one was an infant who died of cardiac arrest due to an attempted tracheostomy (Sales *et al.*, 1957) and another was our second case who died of broncho-pneumonia post-operatively. According to Bale (1950), the cause of death was not mentioned in the remaining two cases. The mortality with surgical treatment is thus about 9% if the malignant tumours are not included, an extremely low figure considering that over half the cases were treated before 1930.

Of the 36 cases in which surgery was not undertaken, 14 were stillborn and one was an adult who died of metastases from a malignant tumour (Bale, 1950). The remaining 21 cases were live, newborn

infants, all of whom died without having had any operative treatment. It is difficult to estimate how many of these infants could have been saved by surgery but, to mention a few instances only, the lack of early surgical treatment was most probably responsible for death in two of McGoon's (1952) cases and in Carter's case (mentioned by Bale, 1950).

Thus the significant facts are that the mortality from operation on benign cases at all ages is low; that more than 25% of all patients died soon after birth without having had surgery; that it is more than likely that many of these infants could have been saved by timely operation.

Hence the first principle in the treatment of these tumours in infants is early operation, especially when tracheal and oesophageal obstruction are present. Delay in surgery, when the respiratory passages are partially obstructed, leads to retention of secretions, atelectasis and broncho-pneumonia. When the tumour does not encroach on the trachea or oesophagus surgery may be postponed, but this is not common.

In the pre-operative phase resuscitative measures such as tracheal aspiration, oxygen and stimulants may be required; laying the infant on the side of the tumour may help to relieve some of the compression and traction on the trachea.

The operation should consist of excision of the tumour and its capsule together with redundant skin. General anaesthesia with intubation should be employed; some authors have employed local anaesthesia (Salviati and Savegnago, 1952) or no anaesthesia at all (Lantuéjoul and Truffert, 1946).

In benign cases, the operation itself is relatively simple since the tumour 'shells out' without much difficulty. Care should be taken when the tumour is loosely adherent to the respiratory passages or thyroid gland since temporary vocal cord paralysis has occurred (Salviati and Savegnago, 1952; Perkins and Pautler, 1953). Caution may be required when, occasionally, the tumour enters the mediastinum.

Tracheostomy without excision of the tumour is not usually possible since the tumour obscures the trachea in many cases. However, tracheostomy has been performed after removal of the tumour (Lantuéjoul and Truffert, 1946; McGoon, 1952) in order to establish and maintain a patent airway.

Post-operatively, meticulous care should be taken in maintaining a patent airway; antibiotics should be given and oral feeding may be carefully commenced fairly soon after surgery. When the thyroid gland is absent or is removed by operation replacement therapy with thyroid extract will be required.

It is not proposed to discuss the management of

malignant teratoma in detail. However, wide local excision of the tumour is obviously mandatory if there is to be any prospect of avoiding local recurrence.

Summary

Cervical teratomas have been defined. Twenty-two new cases have been added to the 60 cases previously reviewed. Two personal cases have been described in detail.

Previous attempts to distinguish thyroid from cervical teratoma have been indicated and a new set of criteria proposed. The tumours usually appeared at birth and were equally divided between the sexes. Several cases have been reported in Negroes.

Histologically tissues from all the germinal layers were found including brain and thyroid tissue. Except for four cases of malignancy (three in adults) all the tumours were benign.

The appearance of the tumour has been described in detail and the likelihood of acute obstructive symptoms of the larynx and oesophagus at birth has been indicated. The tumour caused hydramnios in 18% of cases and occasionally impeded labour. Occasionally congenital anomalies were present in other parts of the body.

The chief points in differentiating the tumour from cystic hygroma, congenital goitre and branchial cyst have been indicated.

The mortality with surgery in benign cases was 9%. On the other hand, all cases not treated surgically died. The principles of surgical treatment have been outlined.

We would like to thank Mr. George Brown and Dr. R. I. Mackay of Salford for permission to publish the first case and Dr. J. K. Steward of the Manchester Tumour Registry for help with the pathological data in that case. We also wish to thank Dr. Harold Dargeon of New York for permission to publish the second case.

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Addendum

Since this paper was written an article has appeared reporting two further cases of teratoma of the neck (Keynes, W. M. (1959). Teratoma of the neck in relation to the thyroid gland. *Brit. J. Surg.*, 46, 466). A summary of tumours reported since 1950 is given, but omits mention of Cases 1-4, 10 and 15-19 (see Table 2). It provides reference to two cases before 1950 which we had omitted (Shattock, S. G. (1882). Congenital tumour of the neck. *Trans. path. Soc. Lond.*, 33, 289; Daniels, D. W. (1928). Congenital tumour of the neck. *Brit. J. Surg.*, 15, 523).

AMOEBIC LIVER ABSCESS IN AFRICAN CHILDREN

BY

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Amoebiasis is common among Africans in Durban, where this hospital alone handles over 2,500 patients each year. Children share in this high incidence of the disease. Many cases are severe and liver abscess is frequently seen.

The purpose of this paper is to compare and contrast the features of amoebic liver abscess in children with those in adults and to discuss clinical diagnosis.

Material

This consists of a series of 53 cases of amoebic liver abscess admitted to the Paediatric Department during a period of seven years from November, 1951. All were proved by demonstration of pus either by aspiration or at necropsy.

Age Incidence. The age distribution is shown in Fig. 1. The youngest was 8 weeks and the oldest 5 years. Seventeen were under 1 year, 10 being less than 6 months old.

Senecal, Larivière, Dupin and Trenou (1957), in reporting four cases of amoebic liver abscess in children, state that Lestrade and Guérineau had found that up to 1956 the world literature contained only 47 reported cases of amoebic liver abscess in children. Since then Torroella, Lopez and Villareal (1956) have described 14 cases in children under 6 years in Mexico.

Although this condition is uncommon in children elsewhere, it is not infrequently seen in African children in Durban.

Sex Distribution. Thirty-two of the 53 cases were males. Torroella *et al.* (1956) described 14 cases in children, of whom 5 were males. It appears that male predominance is less in children than in adults.

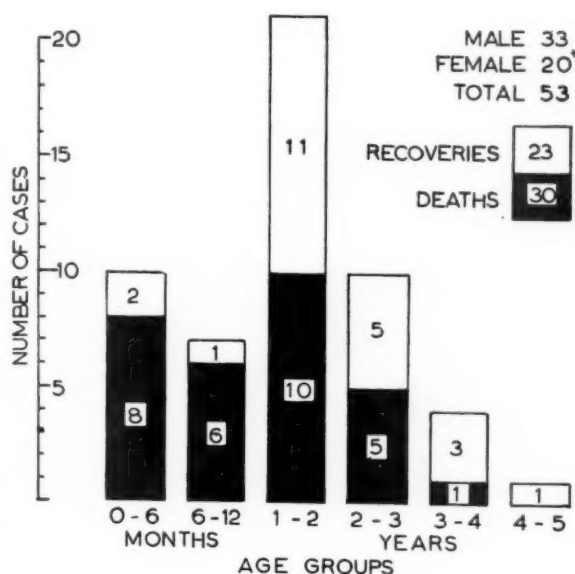


FIG. 1.—Amoebic liver abscess in children. Age incidence and outcome of 53 cases.

Location of Abscesses. The location of abscesses clinically and at necropsy was as follows:

Right lobe	33 (62%)
Left lobe	2 (4%)
Central at junction of lobes of liver	5 (9%)
Multiple	13 (25%)

Abscesses are said to be characteristically single and to occur most often in the right lobe. In this series 75% were single and 25% multiple (Fig. 2). These figures show that the distribution of single abscesses is similar to that reported elsewhere. It seems that multiple abscesses are commoner in Durban African children than is usually the case,

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but this may be due to the high proportion of necropsies.

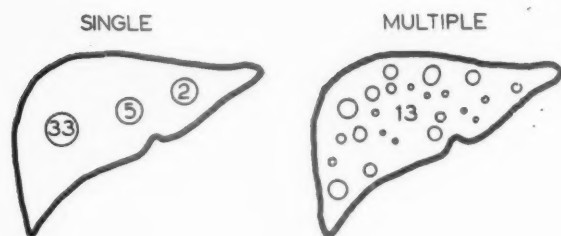


FIG. 2.—Location of amoebic liver abscesses in 53 cases.

Fever. This was present in all cases (Fig. 3). The temperature usually fluctuated between 102 and 103° F. until appropriate therapy was begun. In adults fever is not a constant manifestation of liver abscess (Wilmot, 1949; Lamont and Pooler, 1958). In children, however, it is an important and striking feature.

was observed in 34 cases, and between 30,000 and 43,000 W.B.C.s per c.mm. in six others. Two fatal cases with extremely high counts were found to have single hepatic lesions at autopsy. Three with very high counts recovered and the two lowest counts of 8,000 and 9,000 occurred in children who at autopsy had multiple lesions. These findings do not confirm the opinion that a pronounced leucocytosis indicates multiple abscesses with a bad prognosis (Rogers, 1922).

My findings show that in children the white cell count is more often raised and the elevation is greater than in adults, in whom leucocytosis is present in only 70-80% (Wilmot, 1949; Lamont and Pooler, 1958).

In these children the duration of the history bore no relationship to the level of the white cell count, unlike the findings of Lamont and Pooler (1958).

A normocytic normochromic anaemia was present in 38 cases, the haemoglobin being 7.6 g./100 ml. (range 4.8 to 10.0 g./100 ml.). Anaemia is an important feature of the disease in children and

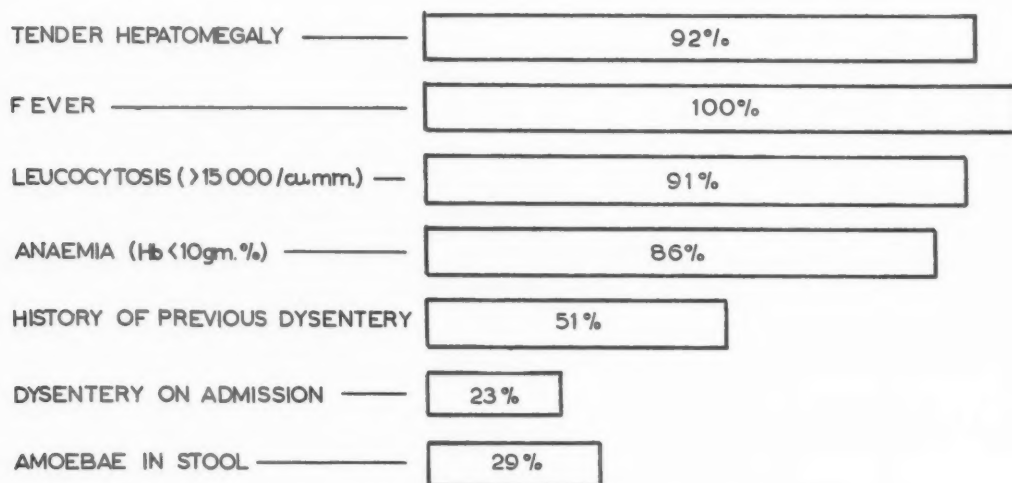


FIG. 3.—Incidence of common clinical findings in 53 cases of amoebic liver abscess.

Tender Hepatomegaly. This was present in all but four cases. It is unusual for the liver not to be enlarged to at least three fingers' breadth below the costal margin. Intercoastal tenderness may be difficult to elicit in infants but direct palpation of the liver is usually exquisitely painful. A palpable mass was present in 40.

Haematological Findings. Blood examination was done in 44 cases. The white blood cell count was raised in 40 (91%). In the remaining four it ranged from 8,000 to 11,000 W.B.C.s per c.mm. Leucocytosis between 15,000 and 29,000 W.B.C.s per c.mm.

rapidly improves with treatment of the primary disease.

Radiological Findings. Radiological examination of the chest was done in 35 cases; 11 (31%) showed elevation of the diaphragm, seven of these having associated pulmonary changes. Figs. 4a and b and 5a and b show the radiological changes in two cases. It seems that radiology is less often helpful in children than in adults, among whom the majority exhibit diaphragmatic elevation (Ochsner and DeBakey, 1943; Wilmot, 1949; Lamont and Pooler, 1958).



FIG. 4a.

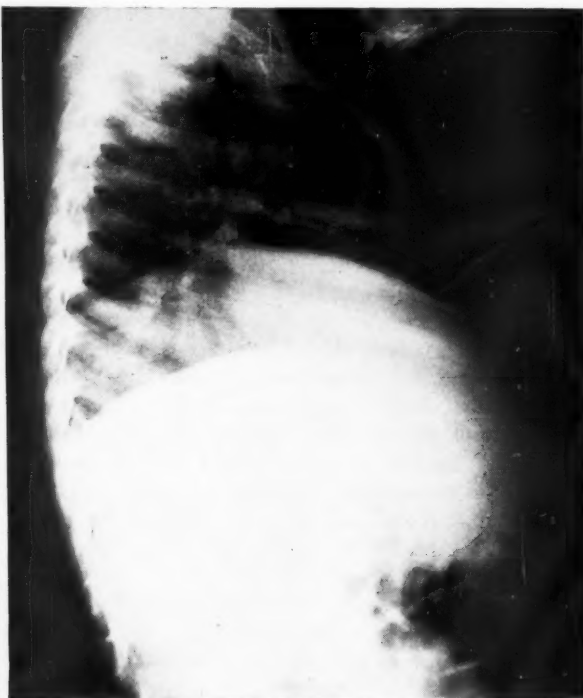


FIG. 4b.

FIG. 4 (a and b).—Radiographs of chest showing marked elevation of right dome of diaphragm before aspiration of large liver abscess (total of 926 ml. of pus removed).

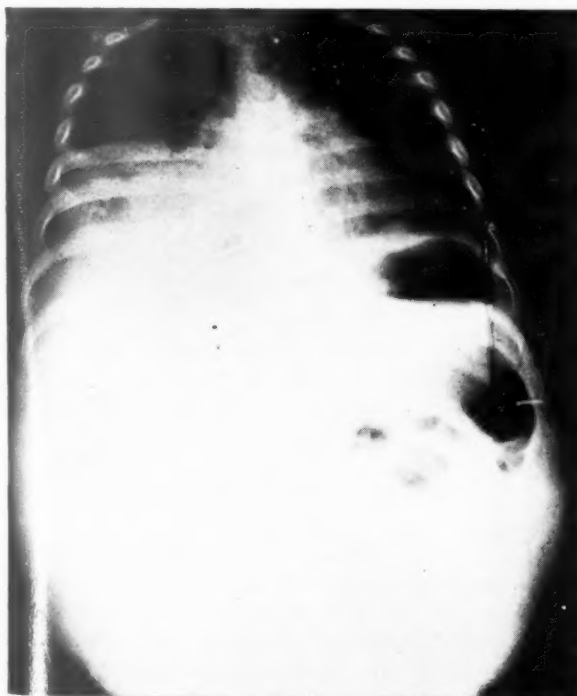


FIG. 5a.



FIG. 5b.

FIG. 5.—(a) Radiograph showing marked elevation of right dome of diaphragm; (b) after aspiration of 80 ml. of pus from liver; air can be seen in abscess cavity.

Dysentery or History of Dysentery. Twelve (23%) of the children had dysentery on admission and a past history of dysentery was obtained in a further 27 (51%). Thus 73% had antecedent or concomitant dysentery, which is similar to the findings in adults.

The absence of amoebae in the stools by no means excludes the diagnosis of amoebiasis, amoebae being found in only 13 (29%) of the 45 in whom stools were examined. Of seven who died before stool examination, three were found to have no bowel lesion at necropsy. In 13 necropsies in which amoebic ulceration of the bowel was found (eight of whom had extensive ulceration) amoebae were found before death in only two.

Nature of Pus. Classical 'anchovy-coloured' pus should not be anticipated as it was usually grey-green or grey-yellow at first aspiration and only at subsequent aspirations took on the pink or red-brown colour. Roach (1958) found that the abscess contents were yellow in over 90% of subjects at necropsy and concluded that 'only rarely at necropsy does the liver abscess contain the "anchovy-type" material considered by many to be characteristic'.

Opinions differ regarding the incidence of amoebae in the abscess contents. DeBaakey and Ochsner (1951) found amoebae in 26% of 263 patients. In my series amoebae were found in the pus in eight (20%) of 40 cases aspirated and at necropsy in 13 (62%) of 21 cases. With recently improved technique, the Amoebiasis Research Unit, Durban, in a series of 71 consecutive liver abscesses in adults, have observed and/or isolated amoebae from 57 (80%) cases (Maddison, 1959). In future, therefore, we may find amoebae in aspiration specimens with greater frequency.

The pus was characteristically bacteriologically sterile in 36 (90%) of the 40 cases aspirated. In four bacteria were isolated from the first aspirate, but in no case did secondary infection occur as a result of aspiration.

Complications

Rupture of Abscess. This occurred in five patients (three fatal). In one, intrapulmonary rupture was followed by clinical improvement and recovery. In another, after two aspirations, rupture occurred through the abdominal wall. This infant made a remarkable recovery as he seemed moribund on admission. Two died shortly after admission from intraperitoneal rupture, and one case died suddenly following rupture of the abscess into the pericardium and pleural cavity.

Brain Abscess. This rare complication was found at necropsy in an infant aged 5 months who had a

massive abscess in the right hepatic lobe and multiple small abscesses in the left lobe. Amoebae were found in the brain abscess which had caused quite extensive cerebral softening.

Jaundice. Lamont and Pooler (1958) found jaundice in six of their 16 fatal cases. In my series it occurred in only one case, autopsy revealing two large abscesses producing mechanical obstruction to the biliary system (Fig. 6).



FIG. 6.—Necropsy photograph of liver from infant aged 4 months. Two large abscesses produced mechanical obstruction of biliary system with large mucocoele of gall bladder.

Mortality

There were 30 deaths, i.e. a mortality rate of 57%. Only two infants, aged 5 months and 7 months, recovered out of the 17 cases under 1 year of age.

The mortality rate in children cannot be assessed since no large series has been reported. In a study of 77 consecutive African patients with liver abscess Wilmot (1949) found a mortality rate of 11.7%. DeBaakey and Ochsner (1951) reported an overall mortality of 22.2%, the mortality in their series being 100% in multiple abscesses but only 11% in those with single lesions. Multiple lesions undoubtedly worsen prognosis for they were present in 12 of the 21 children in whom autopsies were performed. Twelve cases were moribund and died soon after admission.

Treatment

Specific Anti-amoebic Therapy. Excluding the six cases where the correct diagnosis was not made, all received emetine. To those who survived long enough emetine was given for 10 days, the daily dose varying from gr. 1/8 to gr. 1/4, depending on the weight of the patient. Ten received a further seven-day course of emetine. Chloroquine diphosphate was used in an initial dose of 0.5 g., followed by 0.25 g. daily for 15 to 21 days. As chloroquine

therapy alone is followed by a significant relapse rate (Harinasuta, 1951; Wilmot, Powell and Adams, 1958), a combination of emetine and chloroquine may be the best form of treatment. In addition tetracycline or its derivatives and diiodo-hydroxy-quinoline were given when dysentery was present. Antibiotics are of no value in the treatment of liver abscess (Wilmot, Armstrong and Elsdon-Dew, 1952; Wilmott, Powell and Elsdon-Dew, 1958; Powell, Wilmot and Elsdon-Dew, 1959). Penicillin was usually employed while aspiration was being carried out as a precaution against secondary infection.

Supportive Measures. Intravenous fluids and blood transfusions were used when indicated. The maintenance of hydration and electrolyte balance is of paramount importance when serious dysentery is present.

Aspiration. This was done in 40 cases: 12 were aspirated once only, 18 on two to four occasions, and seven on five to seven occasions; three required 12, 13 and 17 aspirations respectively. From the latter case a total of 1,688 ml. of sterile pus was removed.

Surgical Drainage. One 5-month-old infant was treated by surgical drainage with good result. A further infant, after seven aspirations, developed a midline sinus and a residual small abscess was evacuated surgically. Rapid and complete cure followed. The last case in this series was immediately submitted for surgical drainage when bacteria were isolated from the first aspirate and cure followed.

Discussion

In African children in Durban amoebic liver abscess is commoner than elsewhere and for this reason an acute awareness of the condition in childhood is necessary. This condition should always be kept in mind in the differential diagnosis of hepatomegaly, especially tender hepatomegaly, even in the absence of dysentery or a history of antecedent dysentery. The difficulty in determining in a small crying infant whether hepatic tenderness exists is freely admitted. Another feature occasionally making diagnosis difficult is abdominal distension. However, exploratory transcostal needling would appear justified if amoebic liver abscess is suspected, as early diagnosis is one of the most important factors in lowering the attendant high mortality.

The clinical manifestations of amoebic liver abscess in children are similar to those in the adult, except that fever is a more frequent finding. Failure of response to therapy shown by a continuing high fever and increasing anaemia in children with

dysentery or a history thereof should suggest the possible presence of an hepatic complication. However, concomitant or antecedent dysentery can be expected in only about two-thirds of cases. With adequate treatment of amoebic dysentery there is usually improvement of the general condition of the child within about five days. Haematological changes, especially anaemia and leucocytosis, are of value in making a diagnosis. As in the adult, while radiological changes when present assist the diagnosis, their absence does not preclude it.

Most workers state that conservative treatment with amoebicidal drugs and closed drainage by repeated aspiration is best except where secondary infection is present. DeBailey and Ochsner (1951) showed a striking difference in mortality with conservative therapy consisting of emetine with or without aspiration compared with open operation. They advocate open drainage immediately if on first aspiration the abscess is secondarily infected.

Wilmot (1958) considers that the main indications for open drainage are:

- (1) Failure to aspirate pus from patients with suspected liver abscess whose condition is not responding to emetine and/or chloroquine.
- (2) Secondarily infected abscesses which do not respond to aspiration and local and systemic antibiotics.
- (3) In some cases after rupture has occurred, in order to drain the pus from other loci.
- (4) Cases not improving despite repeated aspiration and specific therapy.

In view of the high mortality rate, in retrospect it might have been advisable to undertake surgical drainage in those who required numerous aspirations. In future more thought should be given to those indications and selected cases should be submitted to surgery. Not all cases of amoebic liver abscess require aspiration on specific anti-amoebic treatment. During the period under discussion there were an additional 14 cases of undoubted amoebic liver abscess, but as confirmatory aspiration was not carried out these cases have been excluded from this series.

The management and treatment of amoebic liver abscess in children is basically the same as that advocated for adults.

Summary

Cases of amoebic liver abscess occurring in 53 African children are reported.

The importance of awareness of the condition and early diagnosis is stressed.

The condition can occur at any age, the youngest case in this series being 8 weeks.

There is not the distinct male predominance that is noted in the adult.

The abscesses are frequently multiple in children.

The important clinical features and difficulties in diagnosis in childhood are discussed.

The mortality is high (in this series about 57%) and only by early diagnosis may complications be prevented.

I wish to record my thanks to Dr. H. L. Wallace, Head of the Department of Paediatrics, University of Natal, to Dr. Pauline Klenerman, in whose wards these cases were treated, and to Dr. S. Disler, Medical Superintendent of King Edward VIII Hospital, Durban, for facilities. I am especially indebted to Dr. R. Elsdon-Dew, Dr. A. J. Wilmot, Dr. S. J. Powell and Dr. N. Lamont for much valuable criticism and advice. Finally, I wish to record my thanks to Miss A. Killerby for the photographs and to the staff of the Amoebiasis Research Unit for access to the literature.

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PERIPROSTATIC HAEMATOMA AND PROSTATIC ABSCESS IN THE NEONATAL PERIOD

BY

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The object of this contribution is to draw attention to a hitherto undescribed lesion, peri-prostatic haematoma, and to discuss its relationship to prostatic abscess occurring in the neonatal period. Both disorders have been wholly or partially responsible for a severe but remediable lower urinary tract obstruction in a series of infants observed at The Hospital for Sick Children, Great Ormond Street. The aetiology of the conditions, and even the exact pathological anatomy, remain obscure for, since all cases survived, only clinical data concerning them are available.

Prostatic abscess in an infant has been described on a number of occasions (Campbell, 1929; Szenkier, 1929; Fox, 1934; Alison and Le Tan Vinh, 1952; Boy, Wallon and Luras, 1953). We have also treated a staphylococcal prostatic abscess in an infant, a case previously reported by George (1953), which is now summarized below.

Case 1. A previously healthy boy, aged 1 month, developed a hard red swelling on both sides of the scrotum; four days later he vomited after feeds and his abdomen was distended, due mainly to an enlarged bladder. Catheterization brought a marked but not complete improvement. The following day gross distension of the abdomen recurred and again catheterization released a clear urine. An abscess pointed in the right scrotum and was opened, releasing 7 ml. of thick sticky pus, which on culture grew *Staphylococcus aureus*. Subsequently catheterization was unsuccessful and the boy was transferred to The Hospital for Sick Children. His temperature had been only slightly raised and he was having small frequent green stools with much mucus. On admission the abdomen was distended and rather tympanitic and rectal examination revealed a small rectum compressed anteriorly by a cystic swelling, apparently in continuity with the bladder. The left epididymis was thickened; the right testicle and scrotum were hard with a discharging sinus inferiorly. Enlarged lymph nodes were present in both groins. The blood urea was normal and the urine sterile, but there was a leucocytosis (W.B.C. 21,200, 73% neutrophils). On the same day a suprapubic cystostomy was performed and a

tensely distended, thin-walled bladder was found. A fluctuant swelling was present beneath the trigone, elongating it and extending downwards behind the urethra. The bladder itself was normal. A perineal incision was made immediately in front of the rectum and a sinus forceps was guided into a large abscess cavity by a finger in the rectum. About 2 oz. of thick pus were evacuated. On culture there was a heavy growth of coagulase-positive staphylococci and a few colonies of *Escherichia coli*.

After three days there was a recurrence of the scrotal abscess and a certain amount of greenish-yellow pus was obtained, which on culture again grew *Staph. aureus*. Rectal examination showed some thickening in the prostatic region when the child was discharged on the fifteenth day. Two months later he was completely symptom-free.

There can be little doubt that the abscess in this case arose within the prostatic gland. It was a strictly midline swelling, closely resembling a prostatic tumour, and the simultaneous occurrence of epididymitis confirmed its prostatic origin. As in similar cases occurring in adult life, there must be some doubt as to whether the infection, which was clearly haematogenous, started in the prostate or in the epididymis, and the primary focus outside the genital tract was not identified. The presence of a staphylococcus suggests a skin sepsis, but none was found and the umbilicus was clean.

The cases which we place in the category of peri-prostatic haematoma (Cases 2 and 4, which are reported in full later) present several points of distinction. A mass was present in the pelvis which contained only old blood, sterile in Case 2, and infected with *Esch. coli* in Case 4 at a time when a blood culture also grew *Esch. coli*. The swelling as felt per rectum was lateral rather than median and was broadly based on the lateral pelvic wall, bulging into the cavity of the pelvis from one side only. It was thus distinguishable from a mass arising within the pelvic viscera. It appeared, therefore, that this effusion of blood had occurred in the fascial spaces

alongside the prostate and bladder a little in front of the rectum. No cause of the effusion could be identified, none of these cases had bleeding from any other source and there did not appear to be any coagulation defect. One infant had *Esch. coli* septicaemia in association with a urinary infection and in addition a urethral obstruction due to congenital valves. The possibility of a descending arteritis in the umbilical artery was considered as a source of the haemorrhage but there was no evidence of umbilical sepsis to support this hypothesis.

The clinical findings in Case 3 resembled those in Cases 2 and 4 but the swelling in the pelvis contained pus rather than blood: its lateral position suggested that suppuration might have occurred in a periprostatic haematoma but it could equally have arisen as a metastatic abscess in the prostate. In Case 5 the swelling resolved without surgical intervention; it is possible that an abscess cavity burst into the urethra in this child, suggesting a true prostatic lesion.

Retention of urine was the dominant clinical feature in all these infants. It was abrupt in onset and, although occurring within the first month of life, in only one was there any suggestion of a congenital abnormality. The bladder was tensely distended, the kidneys palpable and the blood urea raised. The urinary obstruction was due to pressure on the urethra and bladder neck: it was relieved as soon as the abscess or haematoma was evacuated. Urinary infection was present at some time in all instances, but probably resulted from catheterization. In Case 4 *Esch. coli* was already present before instrumentation and a septicaemia with severe collapse and dehydration at first concealed the real nature of the condition.

Drainage was obtained through a perineal incision: this method entails least disturbance of other organs but the track is apt to be long and narrow. It was found that refilling of the cavity could be minimized by stripping down the area with a finger in the rectum, and the fourth case settled down within a few days on this routine. Convalescence in all cases has been prolonged and the urinary infection has been difficult to eliminate. Some permanent damage to the upper urinary tract must be anticipated although the blood urea in all cases returned to normal.

Case Reports

Case 2. This boy, a first child, was born at full term on June 18, 1955 in a normal delivery and weighed 8 lb. 12 oz. The mother's pregnancy and puerperal period were uneventful apart from moderate anaemia. He was breast fed for one week, and then thrived on

bottle feeding (N.D. milk) having no complaints until 4 weeks old when, on July 13, he started vomiting after feeds and having diarrhoea with loose greenish stools without mucus or blood. The parents also noticed that the child cried after passing urine, although he had a good stream with no dribbling. On account of worsening of his symptoms, he was admitted to Thurrock Hospital on July 15 and was found to have abdominal distension and a full bladder; catheterization produced 13 oz. of pale clear urine. When catheterized again that evening another 14 oz. were obtained. On July 16 the bladder was again distended up to the umbilicus and the infant's general condition was poor. Catheterization was then unsuccessful: a suprapubic lumbar puncture needle was inserted and 9 oz. of urine were removed.

The child was transferred to The Hospital for Sick Children and on admission on July 16 he did not look well but cried fairly lustily. His colour was fair but he was moderately dehydrated, weighing 9 lb. 4½ oz. There was moderate tachypnoea and a suggestion of meningism but no pyrexia. The abdomen was distended with subcutaneous veins rather more obvious than usual. The bladder was up to the umbilicus but the kidneys could not be felt. Rectal examination revealed a large anterior mass bulging into the rectum. The provisional diagnosis was congenital urethral obstruction. Investigations showed:

(16.7.55) blood urea 134 mg./100 ml.; serum electrolytes: Cl 713 mg./100 ml. (121 mEq./l.), Na 345 mg./100 ml. (150 mEq./l.), K 21 mg./100 ml. (5.4 mEq./l.), CO₂ 21.2 vol. % (9.5 mEq./l.); Hb 86% or 12.73 g./100 ml.

(17.7.55) blood urea 142 mg./100 ml.; urine pale, turbid; S.G. 1016; protein 160 mg.%; deposit: masses of W.B.C.s in uncentrifuged urine; heavy growth of *Proteus* on culture.

(18.7.55.) bleeding time 4 min. 55 sec.; clotting time 1 min. 40 sec.

Dehydration was corrected with intravenous fluids and bilateral pyelostomy was performed for drainage. The following day there was still a palpable cystic mass in the prostatic region and an operation was performed under a general anaesthetic. After catheterization, which obtained 5 oz. of urine, an exploratory needle was introduced through the perineum and entered a cystic cavity from which some dark blood was withdrawn. A small perineal incision was then made and through it 1 oz. of similar material was obtained. This cyst appeared to have no connexion with either the rectum or the lower urinary tract. A rubber drainage tube was left in place in the wound and the urethral catheter was left to drain the bladder. The contents of the cavity showed numerous R.B.C.s; an occasional polymorph but no organisms were seen. On culture there was no growth.

During the following days his general condition improved steadily and his blood urea fell. The left nephrostomy tube was removed on July 18, the right nephrostomy tube on July 22 and the urethral catheter on July 23. At that time the urine was sterile. As there seemed to be inadequate drainage and he was not able to empty his bladder completely, the wound was re-explored on July 26 and another drainage tube was

inserted. A sinogram was performed and outlined the cavity which was unconnected with any of the pelvic organs (Fig. 1). A wound swab showed on culture a light growth of coagulase-positive staphylococci and *Esch. coli*. In the following days the discharge became frankly purulent but diminished progressively in amount, and the pelvic mass gradually subsided. On September 4 he developed gastro-enteritis and he required several intravenous infusions and antibiotic treatment before he finally settled down. When he was discharged on October 2 he was having no difficulty with micturition, and the pelvic mass had practically disappeared, leaving only a rather general induration which extended across both sides of the pelvis.

When re-investigated three and a half years later, the urinary tract was normal on intravenous pyelography and cystoscopy, although he was still enuretic.

Case 3. A premature first-born male child was born on September 17, 1957, by normal delivery. He weighed 4 lb. 14 oz. and looked normal. He thrived on bottle feeding (N.D. milk) and had no complaints until 5 weeks old when, on October 23, he ceased to pass urine. His legs and lower abdomen were moderately oedematous and he vomited after all feeds. On the same day he was admitted to the Whittington Hospital where he was found to have a distended bladder.

He was transferred to The Hospital for Sick Children on October 24, when he looked ill and rather pale and greyish in colour but hydration was fair. He weighed 7 lb. 5½ oz. There was moderate oedema in the legs and lower abdomen, which was rather distended and tym-

panitic; the bladder was felt up to the level of the umbilicus. Both kidneys were easily felt, particularly the right, but did not seem to be enlarged. The penis, testicles and scrotum looked normal. Catheterization withdrew 4 oz. of dirty urine and rectal examination revealed an apparently painless, smooth and rounded mass in the pelvis, which prevented full introduction of the examining finger. The mass was situated rather lower down than would be expected for the bladder, although there seemed to be continuity of the two structures, the bladder wall being thickened and hard. The child's temperature was 96.4° F., but had risen to 101.4° F. next morning. The diagnosis of peri-prostatic abscess was made.

Laboratory investigations gave the following results: (25.10.57.) blood urea 79 mg./100 ml.; serum electrolytes: Cl 578 mg./100 ml. (99 mEq./l.), Na 310 mg./100 ml. (134 mEq./l.), K 20 mg./100 ml. (5.1 mEq./l.); CO₂ 64.7 vol. % (29.2 mEq./l.); Hb 79% or 11.60 g./100 ml.; W.B.C. 29,500; neutrophils 65%; P.C.V. 40%; urine slightly alkaline; protein 80 mg.%; deposits nil; culture (catheter specimen) no growth.

At operation a needle was introduced through the perineum in front of the rectum; it entered the cavity of a peri-prostatic abscess and 20 ml. of thick greenish pus were removed with a syringe. Afterwards the opening was enlarged with a sinus forceps and a corrugated rubber drain was left in place. The pus showed a very large number of polymorphs and gram-positive cocci, which on culture produced a heavy growth of coagulase-positive staphylococci.

Following the operation micturition was normal. The

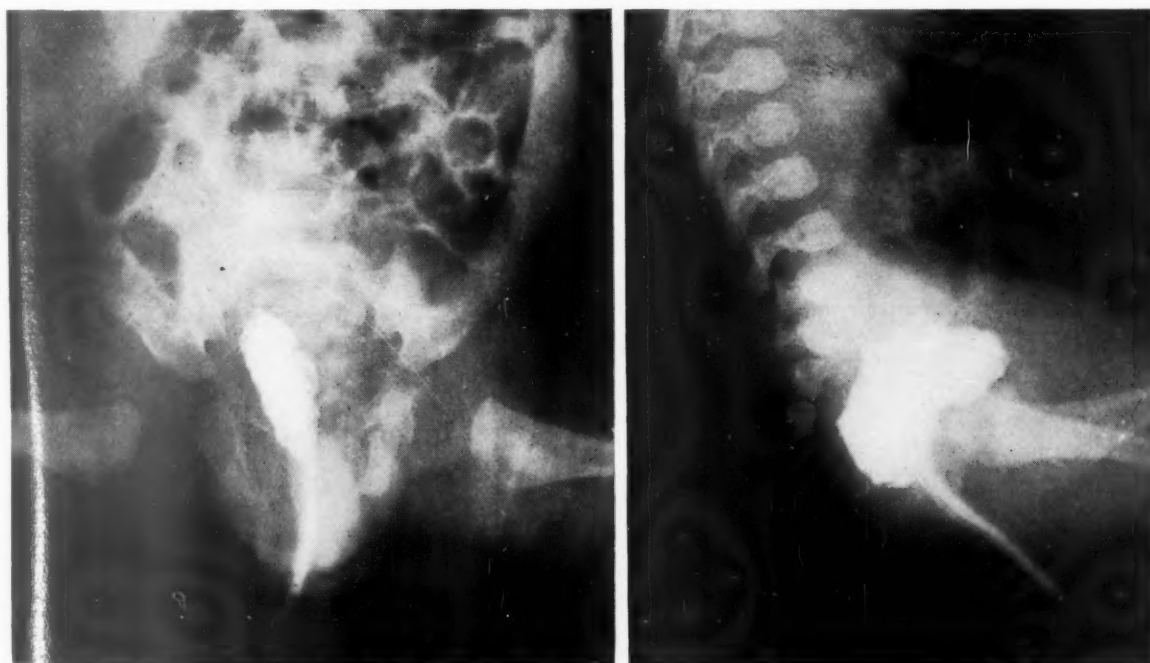


FIG. 1.—Case 2. Sinograms outlining haematoma cavity.

sinus had to be opened with forceps on two separate occasions, but he then had an uneventful convalescence and was discharged on November 9. The perineal wound was healed, he was taking feeds well, gaining weight, and had a good stream of urine. Rectal examination was normal apart from slight induration of the prostatic region.

Eighteen months later his adoptive parents wrote to say that he was in excellent health, and as they were living a long way from London they were not prepared to bring him up for examination.

Case 4. A third child was born at full term on May 21, 1958, in a normal delivery. The mother's pregnancy and puerperal period were uneventful. He weighed 8 lb. 12 oz. at birth.

During the first week his stools were rather frequent, small in amount and brownish in colour, and he lost weight steadily, looking rather lethargic. On June 2 he vomited once before and once after a feed. The vomit was at times projectile, containing some brown material but no definite macroscopical evidence of blood. He was sent to The Hospital for Sick Children with a diagnosis of pyloric stenosis.

On admission under Dr. Wilfrid Sheldon on June 3 he looked rather sallow but his hydration was fair, his weight being 7 lb. 13 oz. The abdomen showed no visible peristalsis and no pyloric tumour was felt. The liver was two fingers below the costal margin with a slightly irregular edge. The kidneys were enlarged and lobulated and the blood urea was 208 mg.%. A routine urine analysis showed infection with *Esch. coli*, and a blood culture performed the same day also showed a heavy growth of *Esch. coli*. Next morning the spleen was palpable and the child was put on Achromycin.

Two days later there was some generalized oedema, the kidneys were still enlarged and a distended bladder was also palpated. The blood urea was still raised and bilateral pyelostomies were performed for drainage. At operation the kidneys were found to be large but looked healthy and the pelves were not unduly distended. On the following day an examination under anaesthesia revealed a smooth round prostatic swelling. A needle was introduced through the perineum and altered blood was aspirated. An incision was made and a large amount of blood evacuated. A corrugated rubber drain was left in the wound and an indwelling catheter was used for bladder drainage. The blood produced on culture a heavy growth of *Esch. coli*.

In the afternoon following operation the child was still pale and lethargic and he was given a small blood transfusion. Next day the prostatic swelling had lessened and some more blood clots were expressed with the help of a rectal finger. The nephrostomy tubes were then removed. He was kept on intravenous fluids until June 10, and by that time his general condition had considerably improved. On June 11, although the kidneys were still palpable and the bladder distended at times, he was able to pass urine with a fair stream.

Subsequently he made only slow progress, interrupted by repeated urinary infections. By July 7 the blood

urea had fallen to 41 mg./100 ml., but micturition was not satisfactory. An intravenous pyelogram then showed considerable bilateral dilatation of the ureters and later an expression cystogram revealed the presence of typical congenital posterior urethral valves. This obstruction was treated endoscopically and normal micturition was restored but persistent urinary infection remained a troublesome feature and in November the excessively tortuous left ureter was shortened and straightened. Following that operation progress was more satisfactory, though there was still a slight pyuria.

In this case, therefore, the effusion of blood only exacerbated a pre-existing congenital obstruction.

Case 5. A first child was born at full term on May 5, 1953, in a normal delivery. The mother's pregnancy and puerperal period were uneventful. He weighed 6 lb. 13 oz. at birth and thrived on breast feeding supplemented by a bottle. He had no complaints until 2 weeks old when he was noticed to have a slight whitish discharge from beneath the prepuce and seemed to have pain on micturition, straining and screaming during the act. The urine looked cloudy, thick and whitish and the stream was reduced to a continuous dribble. On account of worsening of these symptoms, he was admitted on May 29 to Amersham General Hospital under Dr. Dermot MacCarthy, and the mucoid penile discharge was found to contain numerous pus cells. The abdomen was not distended but the bladder was full. On rectal examination there was a tense elastic swelling bulging anteriorly into the rectum, encountered immediately by the palpating finger. Following admission he passed increasing amounts of urine, with pus present macroscopically. A urine specimen showed very numerous pus cells and on culture grew *Staphylococcus pyogenes*. He received penicillin 100,000 units twice daily. On May 30, after passing about 1 oz. of pink pus, his urine became quite clear and pain on micturition almost disappeared. His temperature was never above 99·6° F., and throughout he took his feeds well, never vomiting. At this stage he was transferred to The Hospital for Sick Children. On admission he looked a normal healthy boy with good colour and hydration and weighed 7 lb. 12 oz. No umbilical infection or septic spots were noticed, the bladder was not distended, and the foreskin and urethral meatus were normal, no discharge being seen. Rectal examination showed a normal anus and rectum and a soft but enlarged prostate (more on the right side than on the left). No other relevant findings were detected on clinical examination. Within a week the prostatic swelling completely subsided, leaving only a slight induration. Bowel actions were normal, appetite was good, temperature was normal and the child was gaining weight. Micturition was normal with a good stream of clear urine when the child was discharged on June 6.

Investigations showed: (31.5.53.) blood urea 23 mg./100 ml.; Hb 102% or 14·3 g./100 ml.; R.B.C. 4,290,000; W.B.C. 23,200; neutrophils 53%; urine neutral, no protein; heavy growth of *Esch. coli* and moderate growth of coagulase-negative staphylococci on culture.

Summary

Prostatic abscess and peri-prostatic haematoma are both lesions which cause a severe lower urinary tract obstruction in young infants: they are not necessarily associated with a congenital abnormality and the prognosis is good if the cavity is adequately drained. The abscess is probably metastatic in origin or may follow suppuration in a haematoma, but no satisfactory explanation of the haematoma formation is advanced.

The diagnosis is easily made by rectal palpation after the bladder has been emptied by catheter. A strictly prostatic abscess may be difficult to distinguish from a tumour by palpation but an exploratory needle puncture will settle the issue. The peri-prostatic haematoma is based on the lateral

pelvic wall and does not resemble a visceral swelling.

Urinary retention is relieved by drainage of the abscess or haematoma cavity and neither a urethral catheter nor cystostomy is required as long as the cavity is kept empty. Perineal drainage is satisfactory if combined with daily 'stripping' from the rectum. Chemotherapy is required as an adjunct.

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GENERALIZED BRONCHIECTASIS ASSOCIATED WITH DEFICIENCY OF CARTILAGE IN THE BRONCHIAL TREE

BY

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Bronchiectasis may occasionally affect almost the entire bronchial tree. Such changes can be the result either of developmental defects of the bronchial tree or of acquired inflammatory disease. For example, cystic lung and cystic bronchiectasis can result from both causes.

The purpose of the present paper is to record five patients with a most unusual type of generalized bronchiectasis, and to submit evidence that its basis is deficiency of the cartilage of the bronchial walls, probably developmental in origin.

Material and Methods

The five patients have been studied clinically for periods between three and nine years. Radiological, bronchoscopic, bronchographic and bacteriological examinations have been carried out at suitable intervals. The lungs of one of the two patients who died were examined in the fresh state and then fixed by injecting the bronchi with formalin. Studies consisted of macroscopic dissection of several segmental bronchi and their divisions, and serial histological sections of four lung segments (apical, anterior and posterior basic and lingula of the left lung). The stains used were haematoxylin and eosin, Verhoeff van Gieson and periodic acid stain of Schiff. The bronchi were identified numerically by counting distally from the segmental bronchus (Hayward and Reid, 1952); see Appendix.

Clinical Features

Case 1. J.G. In October, 1949, a boy aged 2½ years was referred to the Royal Children's Hospital with a cough, irregular fever and wheezy breathing, which

developed following an attack of morbilli six weeks previously. Before this he was well and had no serious illnesses. His doctor had made a diagnosis of unresolved pneumonia and asthma, and had unsuccessfully treated him with antibiotics and antispasmodics. He was found to be thin, with slightly cyanosed lips, and his breathing was difficult and audibly wheezy. His chest was barrel-shaped, and inspiratory and expiratory rhonchi and fine crepitations were heard over the entire chest. A radiograph of the chest showed prominent hilar shadows and bronchovascular markings, some haziness in the right middle lobe and lingula and slight pulmonary emphysema. His Mantoux test 1:1000 OT was negative and *Streptococcus viridans* was grown from a small blob of expectorated mucus. Bronchoscopic examination was normal apart from some muco-purulent secretion in both bronchi. A remarkable bronchographic picture was seen on the x-ray screen, the whole bronchial tree from the first division of the segmental bronchus to the fifth or eighth division (depending on the size of the segment) expanded and narrowed with inspiration and expiration (Fig. 1a and b), while the fourth to sixth or eighth divisions of the right bronchial tree were like a series of elongated balloons which were being inflated and deflated (Fig. 2a and b). These changes were more pronounced in the right than in the left lung. At the site of bronchial branching the movement was not so marked. Apart from one or two small areas, no oil entered the fine divisions of the bronchial tree, even though dye was still present in the bronchial tree 40 hours later (Fig. 3a and b).

Treatment with penicillin and sulphonamides and postural coughing led to slight improvement in his general condition but the cough and wheeze persisted and he periodically had attacks of fever and malaise. As he grew older his symptoms lessened and his general health improved. Nine years after the onset he is in fair health but is unable to run without becoming very short-winded, has a constant slight inspiratory and expiratory wheeze and cough. His chest is barrel-shaped with a pigeon deformity and Harrison's sulcus.

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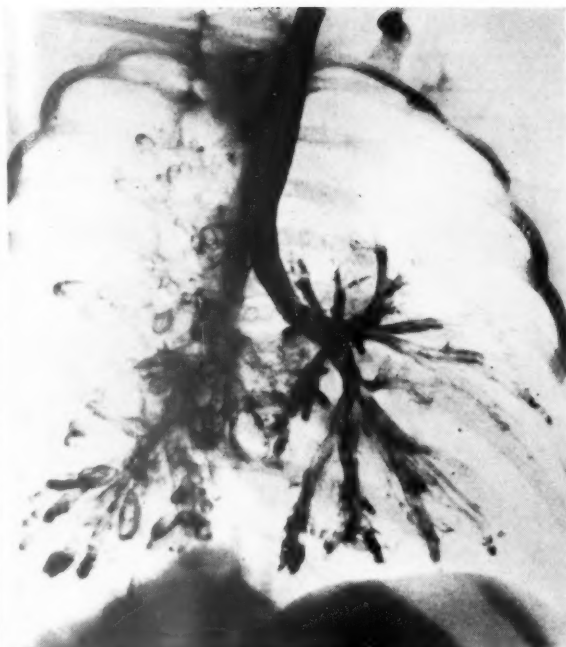


FIG. 1a.—Case 1. J.G. Bronchogram in inspiration showing 'cystic' dilatation of right bronchial tree and cylindrical dilatation of left.

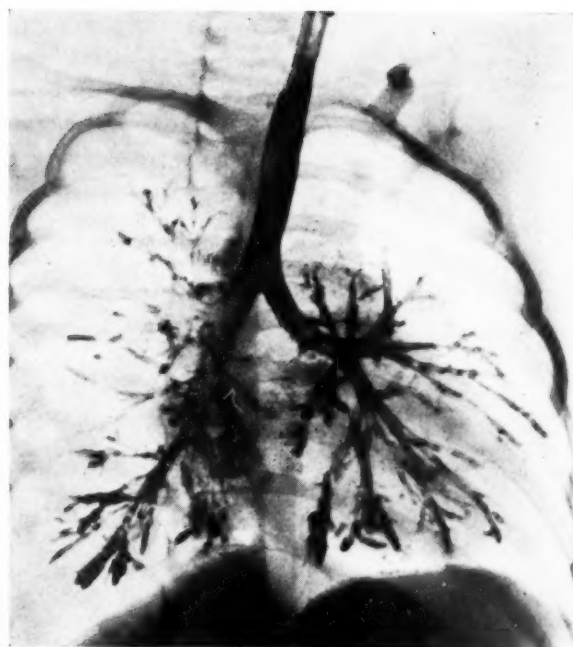


FIG. 1b.—Case 1. J.G. Bronchogram in expiration, showing collapse of bronchi.

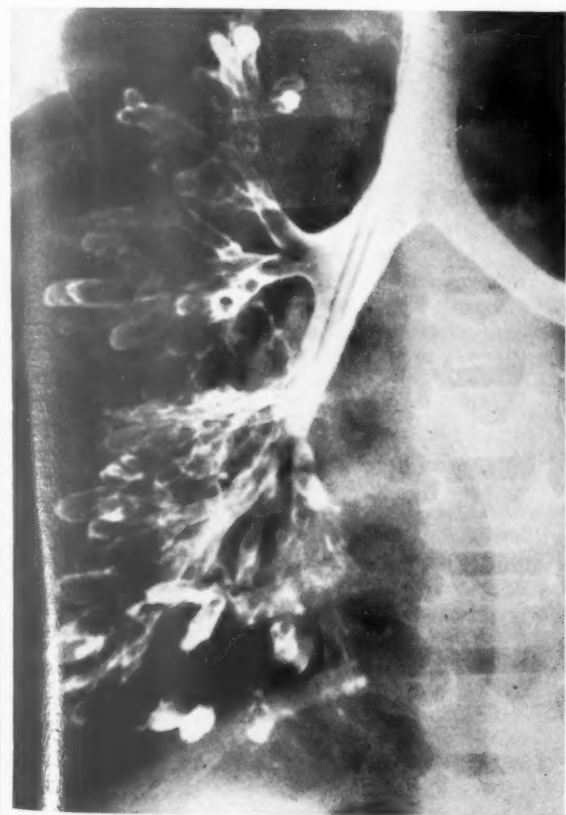


FIG. 2a.—Case 1. J.G. Bronchogram of right bronchial tree in inspiration showing gross bronchial dilatation beyond segmental bronchi but no bronchiolar filling.



FIG. 2b.—Case 1. J.G. Bronchogram of right bronchial tree in expiration showing collapse of bronchi.



FIG. 3a.—Case 1. J.G. Film in inspiration taken 40 hours after Fig. 2a showing retention of dye and no filling of small bronchi.



FIG. 3b.—Case 1. J.G. Film in expiration taken 40 hours after Fig. 2a showing collapse of bronchi.

Case 2. D.S., the first baby of healthy parents, made normal progress until the age of 10 months when he developed a running nose, cough and wheezy breathing. A diagnosis of asthmatic bronchitis was made, but treatment with antibiotics and antispasmodics failed to relieve his symptoms. The cough, wheezing and febrile attacks gradually became worse and his general health deteriorated.

At the age of 2 years 8 months when he was admitted to the Royal Children's Hospital in July 1952 he was ill with distressed wheezy breathing and slight cyanosis of lips and ears. He had a barrel-shaped chest with bilateral Harrison's sulcus, the air entry over the entire chest was poor, and inspiratory and expiratory rhonchi and numerous fine crepitations were heard over the whole lungs. The heart was displaced to the left and the percussion note over the left upper lobe was impaired. The abdomen was distended, the fingers clubbed and he expectorated some mucopus, culture of which grew *Staphylococcus aureus*. A chest radiograph showed collapse of the left upper lobe and mediastinal shift to the left, and the peripheral lung field of the right lung and the left lower lobe

appeared emphysematous. Bronchoscopy was normal apart from a small amount of mucopus in both bronchi. Bronchographic examination was almost identical with that in Case 1, but the bronchiectatic changes were most pronounced on the left side where the left lung was collapsed. Expansion and partial collapse were observed from the first division of the segmental bronchus to the fifth or eighth division, according to the segment, but no dye entered the bronchiolar tree.

Treatment with antibiotics, antispasmodics and postural coughing afforded only slight relief. His condition gradually deteriorated and he died of respiratory failure at the age of 3 years 2 months. Autopsy was refused.

Case 3. J.C. was a healthy baby of healthy parents until she developed pink disease at the age of 14 months. She was left with a slight cough and occasionally had a slight wheeze. At the age of 2 years 3 months she developed measles following which her cough became worse, her breathing difficult and wheezy, her stools pale and offensive and her body wasted. A diagnosis of

fibrocystic disease of the pancreas was made. Following treatment with chemotherapy she very slowly improved.

When seen at the Royal Children's Hospital in May 1953 at the age of 4 years she appeared in fair general health, had a rather barrel-shaped chest, a slight wheeze and produced a little mucopus on posture. Impaired percussion note and tubular breathing were heard over the left lower lobe and scattered crepitations over the entire chest. A radiograph of the chest showed increase in the broncho-vascular markings, collapse of the left lower lobe and somewhat emphysematous peripheral lung fields. Duodenal enzymes and fat balance were normal. Bronchoscopy was normal apart from a little mucopus in the left lower lobe bronchus. The bronchogram showed changes similar to those in Cases 1 and 2 with the exception that in the right lower lobe and pectoral segment of the left upper lobe the bronchial calibre changes during respiration were not so pronounced and there was filling of some of the smaller bronchi and the bronchiolar tree.

From the age of 4 years up to 9½ years she slowly and steadily improved in general health. She has a very slight cough at present and usually no sputum and only wheezes and coughs sputum if she develops a cold or has a feverish attack. These attacks used to occur every few months but now she has them only occasionally. She can run but gets short of wind easily. A ventilatory capacity test at the age of 9 years showed figures indicative of a moderately severe obstructive type of ventilatory defect.

Case 4. A.D., a healthy baby of healthy parents, made normal progress until the age of 10 months when she contracted morbilli. After this she developed a cough, rapid wheezy breathing and would not eat. As these symptoms persisted she was referred to the Royal Children's Hospital in November 1955 aged 1 year with a diagnosis of unresolved broncho-pneumonia. She was moderately well nourished, had slightly rapid laboured respirations with an audible inspiratory and expiratory wheeze. Numerous inspiratory and expiratory rhonchi and fine crepitations were heard all over the chest. A radiograph showed prominent bronchovascular markings and some emphysema in the peripheral lung fields. Culture of a cough swab yielded *Staph. aureus* and *Proteus*. Treatment with one of the tetracycline group of drugs resulted in some general improvement but the cough and wheeze persisted, she continued to run episodes of fever and her signs remained unchanged. Bronchoscopy at the age of 2 years was normal apart from some mucopus in both bronchi. A bronchogram showed symmetrical expansion and collapse of the bronchial tree from the region of the first segmental divisions down to the fifth or eighth branching, according to the segment. Apart from a few areas the dye did not enter small bronchi or bronchioles.

During the two years follow-up her general health has slowly improved. She still has a slight cough and an audible inspiratory and expiratory wheeze, but during the last year has only had two mild feverish attacks. Her chest is deformed with a marked pigeon chest, bilateral

Harrison's sulcus and she breathes with the upper part. She becomes short-winded if she attempts to run.

Case 5. A.W., a premature baby weighing 4 lb. 7 oz., developed a cough and wheeze at the age of 2½ months. The cough and wheeze persisted, he ran frequent febrile episodes and was said to be cyanosed at times. When first seen at the Royal Children's Hospital in December 1952 at the age of 2½ years he was a thin, poorly nourished child (weight 20 lb.) with slightly cyanosed lips and ears. His breathing was difficult and there was a moderately loud inspiratory and expiratory wheeze. The chest was barrel-shaped, movement being predominantly in the upper portion, and numerous fine crepitations and rhonchi were heard all over the chest. No other abnormalities were found. A radiograph of the chest showed increased bronchovascular markings and very few vascular markings in the peripheral lung fields. His Mantoux test 1:1000 OT was negative, his stools did not show any fat globules and culture of a cough swab yielded *Staph. aureus*. Bronchoscopic examination was normal apart from some reddening of the bronchial mucosa and a small amount of purulent exudate in both bronchi. The bronchogram showed that the segmental bronchi down to the fifth or eighth divisions, according to the segment, dilated and narrowed with inspiration and expiration (Fig. 4a and b), but not to the same degree as in the first three patients. Several areas in both lungs showed some bronchiolar filling. Dye was still present in the dilated bronchi 48 hours after instillation.

During the next two years until his death at the age of 4 years 8 months he had a constant cough, increasingly difficult breathing with cyanosis and frequent episodes of fever. Gradually he developed pulmonary hypertension, his heart enlarged, and an angiogram showed some dilatation of the right auricle, right ventricle and pulmonary artery, while the pulmonary tree showed irregular tortuous small arterioles with delayed passage of dye. Cardiac catheterization showed moderate pulmonary hypertension.

Morbid Anatomical Features of Case 5

Pathological changes were confined to the respiratory and cardiovascular systems. In the fresh state the lungs appeared congested and felt nodular. Bronchi distal to the main segmental divisions were dilated and the mucosa of all bronchi was oedematous and inflamed. The pulmonary arteries were dilated and slightly atheromatous, and the heart showed moderate hypertrophy and dilatation of the right ventricle. After formalin fixation further macroscopic and microscopic studies were carried out.

Macroscopic Appearances. The segmental bronchi were normal, but the second and third divisions were dilated, being of similar calibre to the segmental bronchus. Many of the dilated lateral divisions suddenly tapered to a fine thread barely possessing



FIG. 4a.—Case 5. A.W. Bronchogram showing bronchial dilatation in left lower lobe. Film in inspiration.



FIG. 4b.—Case 5. A.W. Bronchogram showing collapse of bronchi in left lower lobe. Film in expiration.

a lumen. Divisions of the axial bronchi distal to the third division gradually tapered, but were still greatly dilated compared with the normal controls (Fig. 5a and b). The most striking feature was the extreme softness of the bronchial walls, which, despite formalin fixation, were as flabby as blood vessels. In nearly all of the bronchi dissected the transition from firm rigid walls to soft easily compressible structures was sudden and occurred along the course of the second or third division. From this point to the periphery the walls remained soft, except where division occurred when a slight resistance could be felt in the acute angle of the bifurcation. In several dissections it was



FIG. 5a.—Case 5. A.W. Dissection showing dilated bronchi, partly unroofed, of lingula and pectoral segments. (Slightly reduced.)



FIG. 5b.—Dissection of normal anterior basic bronchus and its divisions. (Slightly reduced.)

difficult to trace an axial bronchus to the periphery, bronchial branching being dichotomous and forming two divisions of identical calibre. In many instances, however, a true axial bronchus was present (see Appendix).

Microscopical Findings. These were as follows.

SEGMENTAL BRONCHI (FIRST DIVISION BRONCHI). The mucosa showed pseudostratified ciliated columnar epithelium with areas of squamous metaplasia (mucosa less folded than normal) resting on a narrow condensed band of collagen 7-20 μ in thickness. Foci of lymphocytes were present with little apparent relation to the nature or state of the

mucosal cells (*viz.*, pseudostratified, ciliated or non-ciliated, squamous metaplasia).

Muscle coat was present in all bronchi examined. It was very thin in places (30-40 μ) but elsewhere was quite thick (200-300 μ). It was often thin next to cartilage plaques and thicker where cartilage was absent. Beneath the muscle and merging with it was a network of collagen and elastic fibres, thicker and more prominent in areas deficient in cartilage.

Individual plaques of cartilage varied in size and appeared 'chunky', i.e. they were not long and thin as in the normal; in cross-section their size varied from 700 μ to 2,500 μ and, as in the normal, their edges merged with the surrounding fibro-elastic network.

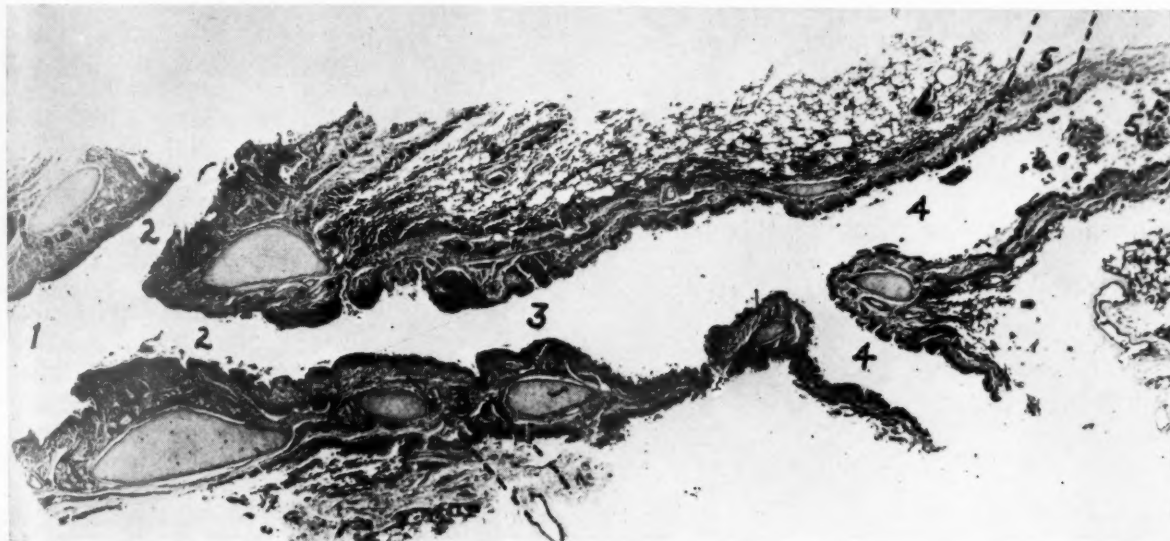


FIG. 6a.—Case 5. A.W. Longitudinal section of segmental bronchus showing cartilage distribution. (Note two bronchi arose out of plane of section. Bronchial divisions are numbered.)

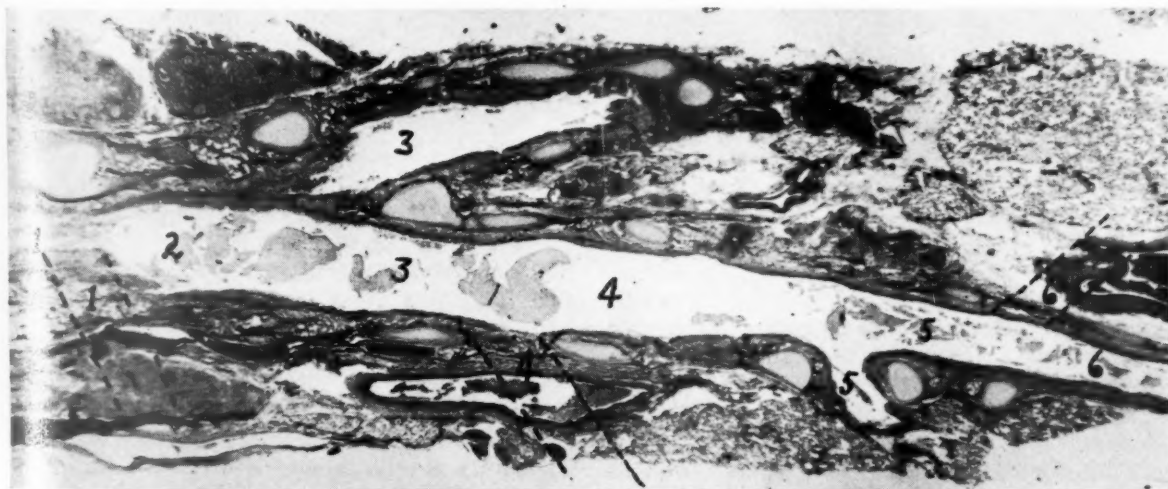


FIG. 6b.—Longitudinal section of segmental bronchus showing cartilage distribution in the normal. Bronchial divisions are numbered. Three bronchi arose out of plane of section.

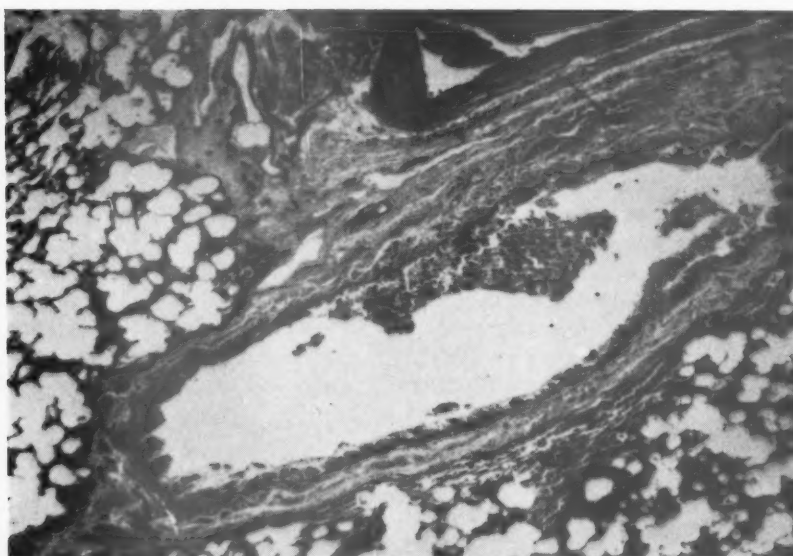


FIG. 7a.—Case 5. A.W. Showing a cross-section of a fifth division axial bronchus. Note complete absence of cartilage in wall. ($\times 25$.)



FIG. 7b.—Normal control, showing cross-section of fifth division axial bronchus. Note cartilage present. ($\times 25$.)

SUB-SEGMENTAL BRONCHI (SECOND AND DISTAL DIVISIONS). More numerous areas of squamous metaplasia were present in the mucosa, otherwise the pattern was similar to that in the segmental bronchus.

Muscle was invariably present, sometimes thin ($30-40\ \mu$) but quite often normal in appearance and thickness. Isolated areas of small round cell infiltration were present, some of which were associated with partial fibrous replacement of muscle.

bronchioles and moderately severe. Vascular thickening was slight, involving the medium-sized and small arterioles.

Discussion

The clinical features in all five children were very similar. The disease commenced in infancy, either insidiously as mild bronchitis or more acutely with morbilli. Persistent cough, wheezy difficult breathing, recurrent febrile episodes and widespread

One must distinguish between the axial bronchus and its lateral divisions, all lateral divisions being devoid of cartilage whereas in occasional cases the third and even fourth division axial bronchi contained isolated cartilage plates. Thus, examination of sections from the anterior basic bronchus (left lung) showed cartilage distribution as follows. The segmental bronchus and the first, second and third division bronchi contained cartilage. In the third division bronchi, the plaques were widely separated and were small. In the fourth division bronchus, very occasional plaques only were visible. Examination of the lingula bronchus showed cartilage as far down as the third division but it was absent distal to this. All other bronchi from the end of the second division showed walls devoid of cartilage except at each point of bifurcation where a small nub of cartilage was present in all cases down as far as the fifth, sixth and seventh division bronchi (Figs. 6a and b; 7a and b).

The following changes were found in the more peripheral parts of the lungs. Bronchiolar obliteration was often severe and extensive (Fig. 8). Bronchioles were far less numerous than in the normal controls. Some that had been recently obliterated were still recognizable, but many were represented only by small areas of scarring. Emphysema was focal, related to obliterated

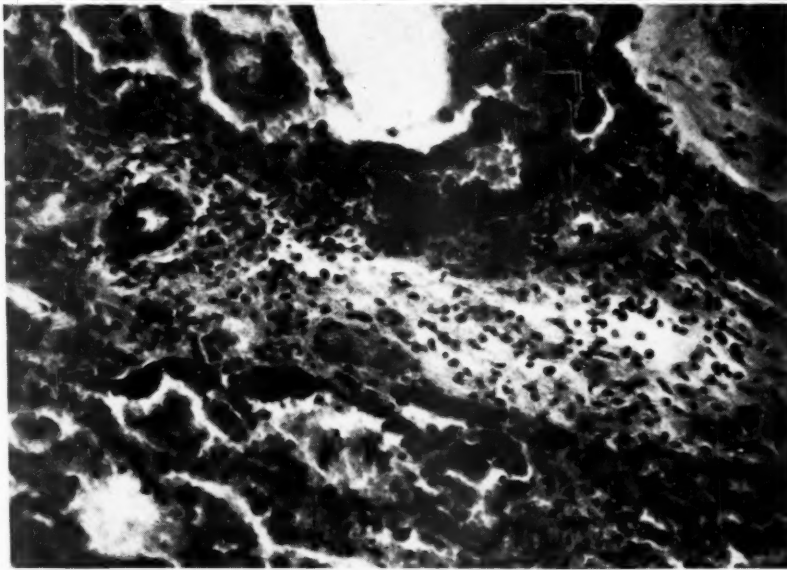


FIG. 8.—Case 5. A.W. Showing bronchiolar obliteration. ($\times 125$)

inspiratory and expiratory rhonchi and crepitations were the main clinical features. The chest was deformed as a result of diffuse bronchial and bronchiolar obstruction and pulmonary emphysema. As the clinical pattern and physical signs were those of chronic or subacute bronchiolitis with recurrent exacerbations, it was no wonder that a diagnosis of asthmatic bronchitis, or non-specific bronchiolitis, or fibrocystic disease of the pancreas was made.

The course of the disease varied considerably. In two patients it was steadily downhill, death occurring at the ages of $4\frac{3}{4}$ and 3 years. Both patients died of progressive respiratory failure, the result of chronic infective bronchiolitis and pulmonary hypertension. One of the three living children is in good health, the only symptoms being a little cough and breathlessness out of proportion to the degree of physical activity. The other two are severely limited, any active exertion resulting in breathlessness. As these children have grown older, infection has become less and their general health correspondingly improved.

The clinical features and bronchographic appearances of Case 1 suggested that expansion and narrowing of the bronchial walls with respiration was due to considerable structural weakness. Lack of cartilage seemed to be the probable structural weakness as similar expansion and collapse of the walls of the trachea and main bronchi had been observed when cartilage was absent from maldevelopment (Ferguson and Neuhauser, 1944; Evans, 1949; and Holinger and Johnston, 1957).

The gross morbid anatomical findings in Case 5 revealed dilatation of the sub-segmental bronchial divisions which were soft to feel and easily compressed, a marked contrast to the normal controls. Serial histological examination disclosed that the cartilage was deficient or absent along the walls in most cases from the third division down, but in small numbers was present in the angle of bifurcation of the bronchi. This deficiency in cartilage in the bronchial walls readily explains the physiological defect observed under the x-ray screen.

The problem is whether this defect is a developmental one, or whether it is secondary to infection. The available evidence favours a primary developmental origin for the following reasons. The lesions were surprisingly uniform, involving almost the entire bronchial tree from the second or third segmental division downwards. The principal defect in the structure of the bronchial wall was in the amount and distribution of cartilage. Had the cartilage been destroyed by inflammation, other structures would almost certainly have been affected, e.g. muscle and elastic tissue, but there was little evidence of this. Again, if inflammation had caused dissolution of cartilage in the walls of the bronchi, one would expect to find several bronchi in which no cartilage at all was present. In fact, however, in all cases where a division occurred one could find a small piece of cartilage at the bifurcation, although the walls themselves remained deficient. Examination of the bronchograms shows a 'nipping in' at the site of branching of the bronchi,

corresponding presumably with this small piece of cartilage.

In acquired bronchiectatic lesions cartilage destruction rarely extends up to the first and second segmental divisions, and then never in a uniform manner. Several patients examined in the present group soon after the onset of the disease showed gross bronchographic changes. The duration and the severity of the clinical infection was too short and too mild to result in such gross structural changes in the bronchial walls or to destroy the cartilage and cause 'flapping' during respiration. In no single case of bronchiectasis due to acquired disease have we seen changes comparable with those in these patients. We therefore presume that the cartilaginous defect is a developmental one and that the symptoms of chronic cough, wheezing febrile episodes and later pulmonary emphysema, pulmonary hypertension and respiration failure in two patients were consequent on chronic secondary infection in the bronchiolar tree.

Summary

Five children with an unusual type of generalized bronchiectasis are described.

The clinical features of chronic cough, wheezy breathing and febrile attacks associated with widespread clinical signs in the chest and pulmonary emphysema were easily confused with asthmatic bronchitis, or chronic non-specific bronchiolitis or fibrocystic disease of the pancreas.

The clinical and radiological features in the five patients and the morbid anatomical findings in one suggest that the underlying basis is maldevelopment in the cartilage of the bronchial tree.

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APPENDIX

The lungs of five children of approximately the same age as Case 5 were examined by macroscopic dissection and by serial section of segmental bronchi and their divisions to establish a normal pattern for children of this age group (Gray (1954), Hayek (1953), Miller (1937)). The results are summarized below.

Macroscopic Findings

Method. Fixed lungs were dissected with fine scissors commencing at the segmental bronchus, which was called the first division bronchus (see Fig. 9). Any branches arising from this were counted and the dissection was carried as far as possible into the periphery of the lung.

Findings. The number of divisions of any segmental bronchus depended on the distance between the origin of the bronchus and the lung tissue it supplied. It was greater in longer bronchi than in short, e.g. lingula, with 10 macroscopically visible bronchial divisions, and pectoral, with five to six macroscopically visible bronchial divisions.

Divisions were of two types. Larger bronchi arose at a very acute angle. Small bronchi generally arose at a much greater angle from the parent trunk (lateral bronchi of Hayward and Reid, 1952).

The concept of an axial bronchus (Hayward and Reid, 1952) was not always easy to demonstrate. True dichotomous branching was common, the resulting bronchi being of similar calibre and coursing to the

periphery, each giving off approximately the same number of divisions (see Fig. 5b).

In general, however, a main or 'axial' bronchus could be followed from which lesser bronchi arose.

The bronchi in the fixed state were firm and elastic.

Circumferential cartilage plaques were present in all segmental bronchi and distally for three to six divisions, depending on the length of the axial bronchus.

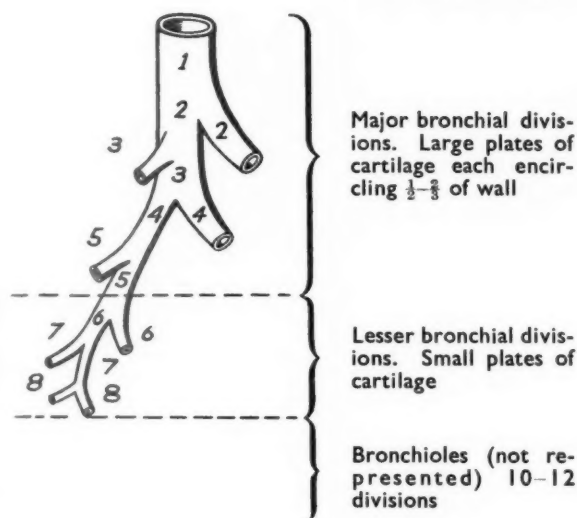
Isolated cartilage plaques occurred in the walls of bronchi from the fourth to the tenth divisions, although they were difficult to see in the more peripheral divisions and their presence had to be confirmed by histological examination.

Microscopic Findings

Serial sections were examined in continuity and all the branches arising from an axial bronchus were counted and an accurate assessment made of their cartilage content. The findings confirmed those made macroscopically.

Mucosa. Regular ciliated columnar epithelium pseudostratified down as far as the smaller bronchioles when it tended to become simple columnar in type. Mucosa rested on a condensed layer of collagen and merged with the underlying collagen network around mucous glands, muscle and cartilage.

Muscle. This occurred in regular fasciculi beneath the mucosa and varied in thickness with the bronchi exam-



L. Post Basic Br.

FIG. 9.—Sketch of a typical normal bronchus and its divisions. Diagram shows method of numbering bronchi and distribution of cartilage in them.

ined (from 50μ up to 500μ). Muscle composed only a small portion of the thickness of the walls of the larger bronchi ($\frac{1}{8}$ to $\frac{1}{10}$) and slightly more ($\frac{1}{3}$ to $\frac{1}{4}$) of the more distal divisions.

Cartilage. In the larger bronchi (in general divisions 1-6) this was present as large plaques each partly encircling the lumen (so-called circumferential cartilage plaques). Their thickness varied greatly, being greater

the larger the bronchus, and generally ranging from $300-1,000\mu$ (Fig. 6b).

In the lesser bronchi (axial divisions distal to the fourth or fifth, and most of the lateral bronchi) the cartilage was distributed sporadically in the wall as isolated bars joined by a condensation of collagen and elastic fibres. A cross-section of such a bronchus would reveal two to four small plaques around the circumference. Their thickness averaged $100-300\mu$. Such cartilage plaques could be found distally as far as the sixth to tenth division, depending on which segment was being examined.

Bronchioles. The transition from bronchus to bronchiole was usually clear. Two criteria were used (a) cessation of cartilage, and (b) relation to surrounding lung. Thus, bronchi were always surrounded by a condensate of collagen in which ran several vessels, lymphatics and nerves, whereas bronchioles lay in intimate relation with lung parenchyma and lacked this collagenous mantle (Engel, 1947). In general the small peripheral bronchi contained cartilage in their walls, but this was felt to be a less reliable criterion than the latter.

On these criteria bronchiolar divisions numbered 10-12 in most cases.

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SYMMETRICAL PERIPHERAL OEDEMA IN INFANTS

BY

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Oedema is a common occurrence in newborn infants, particularly when they are premature. The seven patients, brief clinical accounts of whom appear below, appear to fall into a separate group.

Case Reports

Case 1. A male child was born in 1949 at term following a normal pregnancy and labour. His birth weight was 9½ lb. Swelling of the feet was noted soon after birth. He was breast fed for two months and then reared on dried milk.

On examination at the age of 6 weeks symmetrical pitting oedema of both feet extending a short distance up the legs was present. The hands were spared and no other abnormalities were found. B.P. was 80/50.

INVESTIGATIONS. Urine was repeatedly negative for albumin and deposit.

Hb was 70%, R.B.C. 3,500,000 per c.mm., W.B.C. 12,600 per c.mm. (neutrophils 44%, lymphocytes 49%, eosinophils 2%, monocytes 6%).

Plasma proteins were 6.5 g. per 100 ml. (albumin 4.6 g. per 100 ml., globulin 1.9 g. per 100 ml.). Blood urea was 30 mg. per 100 ml.

Biopsy from the dorsum of the foot showed that the epidermis was rather thin with oedema. The rete pegs were somewhat diminished and the corium a little thickened with some increase of collagen. There was slight perivascular infiltration with lymphoid cells.

The oedema had vanished by the age of 18 months, while growth and development proceeded normally. When last seen at the age of 8 years the child was obese, weight 100 lb. (mean 59½ lb.), height 55 in. (mean 50 in.), but was otherwise normal.

Case 2. This girl was an only child, although the mother had had two previous miscarriages. She was born in 1950, two weeks prematurely, after an uneventful pregnancy with a birth weight of 6 lb. The mother was stated to have had slight swelling of the left foot all her life, and her mother was said to have had oedema of the feet for many years. No swelling was found in the case of the mother, and the grandmother had bilateral but unequal oedema of the feet associated with varicose veins. Both women appeared otherwise healthy.

On examination at the age of 6 weeks the child was healthy apart from symmetrical pitting oedema of the

feet and lower legs, which tapered off about half-way to the knees. The hands were affected to a lesser degree.

INVESTIGATIONS. Urine was free from albumin and abnormal deposit and there was no abnormal amino-aciduria.

Hb was 80%, R.B.C. 4,500,000 per c.mm., W.B.C. 11,200 per c.mm. (neutrophils 43%, lymphocytes 51%, monocytes 6%). Blood urea was 35 mg. per 100 ml., blood calcium 11.2 mg. per 100 ml., serum phosphorus 5.6 mg. per 100 ml. Plasma proteins were 6 g. per 100 ml. (albumin 4 g. per 100 ml., globulin 2 g. per 100 ml.).

The oedema finally disappeared at the age of 4 years. She remained healthy apart from pneumonia when 7 years old. When seen at the age of 8 years a scraping of the buccal mucosa showed a female chromatin pattern. She was small, weight 46 lb. (mean 58 lb.), height 45 in. (mean 49½ in.), and the only other abnormality found was dystrophy of the little toenails. Bone age at this time was one to two years behind the chronological age.

Case 3. This girl, a third child, was born in 1951, the older two siblings being normal. She was said to have been born at term, but weighed only 4 lb. 11 oz. at birth. Pregnancy and labour were normal. Her feet and hands were noticed to be swollen at birth. She was fed from birth on dried milk.

When examined at the age of 2 months she weighed 7 lb. 2 oz. She had symmetrical pitting oedema of the feet and lower parts of the legs and the hands. There was slight webbing of the neck, a low hair-line, high arched palate and rudimentary nails. Signs of coarctation of the aorta were present.

INVESTIGATIONS. Urine was repeatedly normal. Blood urea was 38 mg. per 100 ml., serum cholesterol 135 mg. per 100 ml. Wassermann reaction was negative, and a chest radiograph was normal. Radiological bone age was normal (aged 7 years). A scraping of the buccal mucosa at the age of 6 years was chromatin-negative, suggesting the male sex.

When last seen at the age of 7 years she was mentally retarded and was attending an occupation centre. Her height was 44 in. (mean 47 in.) and her weight was 48 lb. (mean 51½ lb.). The oedema of the hands disappeared in the first year, but that of the feet lingered until she was 5. The other abnormal features were more pronounced, and the chest was broad with widely spaced

nipples. The signs of coarctation of the aorta were present with blood pressure in the arms 150/90 while the femoral pulses were not felt.

Case 4. A female child was born in 1954, two weeks prematurely, after an uneventful pregnancy. Her weight at birth was 6½ lb. She is the third child and the two older children are normal. She was admitted to hospital at the age of 6 weeks on account of a respiratory infection.

On examination there was symmetrical pitting oedema of the feet and lower parts of the legs and of the hands and wrists, which the mother stated had been present from birth. In addition slight webbing of the neck was present and she had dystrophy of the toenails.

INVESTIGATIONS. Urine was normal with no abnormal amino-aciduria. Hb was 85%. The plasma proteins rose from a total of 4.8 g. per 100 ml. at 2 months to 6.5 g. per 100 ml. at the age of 1 year. On each occasion the electrophoretic pattern showed a normal proportion of albumin and globulin. Serum bilirubin was 0.3 mg. per 100 ml., serum alkaline phosphatase 21.5 K.A. units, thymol turbidity 1 unit, serum sodium 320 mg. per 100 ml., serum calcium 10.6 mg. per 100 ml., serum phosphorus 6 mg. per 100 ml.

Examination of a scraping of buccal mucosa showed that the chromatin pattern was of male type.

The oedema of the hands disappeared by the age of 12 months, but that of the feet continued until she was nearly 3 years old. With the passage of time other abnormalities became apparent, notably low hair line, 'shark' mouth, ear deformities, anti-Mongolian slant to the eyes and broad chest with widely spaced nipples. She has remained small and at the age of 3 years 11 months weighed 25½ lb. (mean 35½ lb.) and was 36½ in. in height (mean 39½ in.). The blood pressure has always been normal and the bone age has corresponded with the chronological age.

Case 5. This boy was the third child of healthy parents. The two older siblings were healthy. He was born normally at term in 1954 after an uneventful pregnancy, his weight at birth being 7 lb. Symmetrical oedema of the feet and lower parts of the legs and, to a lesser degree, of the hands was noticed just after birth. The only other abnormality observed was dystrophy of the toenails.

INVESTIGATIONS. Urine was free from abnormal constituents and there was no unusual amino-aciduria. Hb was 90%, W.B.C. 6,500 per c.mm. (neutrophils 45%, lymphocytes 45%). Blood urea was 34 mg. per 100 ml. and the plasma proteins varied from 5.9 g. per 100 ml. at 2 months of age to 6.9 g. per 100 ml. at 8 months. The albumin/globulin ratio and electrophoretic pattern were normal on each occasion.

Biopsy from the dorsum of the foot showed rather thick epidermis with somewhat marked keratinization. The corium showed no inflammatory reaction.

Examination of a scraping of the buccal mucosa showed a chromatin pattern of male type.

Since then he has developed normally and the oedema finally disappeared by the age of 3½ years. At 4 years of age he was small, weighing 31½ lb. (mean 37½ lb.) and

his height was 36½ in. (mean 40 in.). The bone age was equivalent to his chronological age and the highest blood pressure recorded was 90/50.

Case 6. The only child of healthy parents, this girl was born in 1955 at term after a normal pregnancy and labour, her birth weight being 8½ lb. Symmetrical pitting oedema of the feet, lower legs and hands was noted at birth. The only other abnormalities found were a defect of the left pinna and dystrophy of the toe-nails, especially of the little toes. She was fed on dried milk from birth.

INVESTIGATIONS. Urine was repeatedly free from albumin and abnormal deposit and amino-aciduria was normal for her age.

Blood urea was 40 mg. per 100 ml., serum sodium 310 mg. per 100 ml. and serum potassium 22 mg. per 100 ml. The plasma proteins were 5.9 g. per 100 ml. (albumin 3.9 g. per 100 ml., globulin 2.0 g. per 100 ml.). The electrophoretic pattern was normal and the Wassermann reaction was negative.

The chromatin pattern from a scraping of buccal mucosa suggested the female sex.

At the age of 2 weeks adrenocorticotrophin, 10 units of the gel daily, was tried. This was stopped after three days as the oedema became more marked.

She has since developed normally both mentally and physically. Her blood pressure has never been raised, and when last seen at the age of 3 years 2 months it was 90/50. At that time she weighed 35 lb. (mean 31 lb.) and her height was 36 in. (mean 37½ in.). The oedema of the feet was still present though less marked. That of the hands had cleared by the age of 3 years. Her bone age was normal.

Case 7. This girl was the fifth child of healthy parents; the four elder siblings were quite healthy. She was born in 1955 at term, birth weight 5 lb., following a normal pregnancy and labour. Swelling of the feet was noticed at birth and the hands were stated to be swollen at intervals. She was fed on dried milk from birth.

On examination at 2 months of age she had symmetrical pitting oedema of the feet extending about half-way up the legs towards the knees. Mild pitting oedema of the backs of the hands was also present. In addition slight cyanosis of the nail beds and dystrophy of the toe-nails were seen. No other abnormalities were found.

INVESTIGATIONS. Urine was repeatedly free from albumin and abnormal constituents and there was no unusual amino-aciduria.

Hb was 85%, W.B.C. 6,500 per c.mm. (neutrophils 50%). Blood urea was 40 mg. per 100 ml., serum cholesterol 120 mg. per 100 ml., E.S.R. 12 mm. in one hour (Wintrobe). The plasma proteins were 6.4 g. per 100 ml. (albumin 4.2 g. per 100 ml., globulin 2.2 g. per 100 ml.). The electrophoretic pattern was normal.

A skin biopsy from the dorsum of the foot showed hyperkeratosis and mild parakeratosis with slight acanthosis. The deepest vessels of the corium were invested by an infiltrate of tissue cells, a few plasma cells and neutrophils.

A scraping of the buccal mucosa was taken at the age of 2 years. The chromatin pattern was of male type.

When last seen at the age of 3 years 4 months her height was 31½ in. (mean 38 in.) and she weighed 23½ lb. (mean 33½ lb.). Her blood pressure was 100/60. The bone age was normal. Slight oedema of the feet only remained.

All these children had one feature in common, namely oedema, always of the feet and usually to a lesser degree of the hands, which had been present from birth. Pitting was always present and there was no discolouration of the skin nor evidence of circulatory disorder. The swelling of the lower extremities presented a rather typical appearance, being most marked over the dorsa of the feet. It tapered away up the legs to finish below the knees, resembling well-fitting field boots. It was always symmetrical. The oedema tended to disappear from the hands first, and to vanish from the legs in the first few years of life. In five children it has disappeared completely, while in two, both aged 3 years, it is still present but decreasing.

The marked similarity of the swelling without constitutional upset in all these seven patients suggests that all are suffering from the same disease, which has not occurred in other members of their families. In one instance the mother and grandmother were said to have suffered from swelling of the feet but no oedema was found in the case of the mother while the grandmother's oedema was associated with varicose veins, quite unlike the self-limiting disease seen in these children.

Of these seven children, five were undersized for their age when examined in later years. Despite the inferior growth, in only one of them was there a retardation in bone age (one to two years at the age of 8).

Five showed dystrophy of the toenails. This was confined to the toes and was most marked in the little toes. It was always symmetrical. The nails were small, deformed and had a brown hue.

Finally, in three of the five girls examination of the chromatin of the cells in a scraping of buccal mucosa showed the nuclear sex to be male. In the other two girls and the two boys the chromatin pattern corresponded with the morphological sex.

Discussion

The usual causes of oedema in the young infant can be dismissed. There was no evidence of heart or kidney disease, and prematurity was not a factor. Hypothermia was not seen and arthritis was not a feature.

Besides these well-known types of oedema the

earlier literature contains records, often in the form of single case reports, of oedema involving the extremities of newborn children. Confusion resulted from the use of such terms as 'trophic' and 'lymphangiectatic' oedema, 'scleroedema' and 'elephantiasis'.

Three names are particularly associated with these early accounts.

Nonne (1892) described a family with swellings of the lower limbs which were firm, fleshy and non-pitting (congenital hereditary elephantiasis).

Milroy (1892) gave an account of 22 persons among 97 members of one family with congenital 'trophic' oedema of the extremities. The condition was hereditary, permanent and unaccompanied by constitutional disease. The oedema affected one or both legs and might extend up to Poupart's ligament but not beyond. In 21 of the 22 cases the condition was present at birth.

Meige (1898) wrote of a family of eight, whose members suffered from chronic oedema of the legs. The condition was not congenital and usually appeared at about puberty.

Volz (1938) gave a summary of the literature on oedema of the newborn baby up to that time, and described an infant similar to those described here. In addition his patient had bilateral epicanthus and loose skin at the nape of the neck. He listed 12 other somewhat similar cases recorded up to that date.

From this clinical medley Mason and Allen (1935) differentiated one group which they called congenital simple lymphoedema. They described five patients in each of whom the oedema was congenital, affected one limb only and was persistent. The unilaterality and non-familial incidence differentiated them from congenital, familial lymphoedema or Milroy's disease, of which they confessed they had yet to see an example.

The histological features of their cases were characteristic. The subcutaneous fat was replaced by enlarged lymphatic vessels and by fibrous tissue.

These features exclude such a diagnosis in these seven children in whom the oedema was always symmetrical and in whom biopsy failed to reveal the characteristic findings.

Bonnevie (1932, 1934) showed that multiple malformations of the head and extremities appeared as a recessive trait in a race of x-rayed mice—Bagg-Little strain (Bagg and Little, 1924). She showed that these deformities arose as a result of the excessive escape of cerebrospinal fluid through the anterior foramen, an opening in the roof of the fourth ventricle. This excess fluid accumulated as myelencephalic blebs in the neck and then migrated

under the epidermis and eventually reached the extremities. Abnormalities resulted from the effects of pressure caused by these accumulations.

Ullrich (1936) adapted this theory to explain a number of apparently unconnected congenital defects in the human being. These were particularly unilateral deficiency of the pectoral muscles and motor cranial nerve defects as well as various abnormalities of the hand (club-hand). They were attributed to arrest in the migration of myelencephalic blebs. He also considered that unilateral webbing of the neck, congenital lymphangiectatic oedema and certain other defects, such as dystrophic nails and hypoplastic nipples, should be included in the wandering bleb hypotheses. These abnormalities were grouped together as the status Bonnevie-Ullrich, asymmetrical type.

In succeeding years this conception was expanded and, under the title of symmetrical status Bonnevie-Ullrich, a number of seemingly diverse defects was assembled. The most important of these was bilateral webbing of the neck (pterygium colli) accompanied by low hair line, preference for the female sex, loose skin, epicanthus, sagging eyelids, 'shark' mouth, abnormalities of the ears, high arched palate, cubitus valgus, defects of the nails, some degree of dwarfism and sexual infantilism, 'mushroom' epiphyses of the long bones, increased digital markings of the skull and oedematous swellings of the neck and extremities at birth which tend to disappear with the passage of time (Ullrich, 1949). Ullrich has since conceded that the wandering bleb hypotheses can no longer be regarded as applicable to the symmetrical, as opposed to asymmetrical, type of the status.

Independently Turner (1938) described seven girls from 15 to 23 years of age, each of whom showed a triad of infantilism, webbing of the neck and elbow deformity. As Ullrich remarked, these features comprise only some of the characteristics included by European authors in the symmetrical form of status Bonnevie-Ullrich. Yet writers of the English-speaking nations commonly refer to this complex as Turner's syndrome.

In the last 10 years further additions to the status have been suggested (Rossi and Caflisch, 1951; Silver, Kiyasu, George and Deamer, 1953). Terminology has been varied and largely centred on the question of sexual infantilism. The latter has received much interest since the demonstration by Moore, Graham and Barr (1953) that the genetic sex of body cells may be determined by a study of the nuclear chromatin. Use of this technique has shown that the majority of the affected patients, though morphologically girls, are genetically of the

male sex and have gonadal hypoplasia. In children examination of sections of the skin or scrapings of the buccal mucosa have enabled a correct diagnosis to be made before the absence of the normal changes occurring at puberty would draw attention to the condition. Examples in early life have been described by Silver (1956) and Grumbach (1957). The patients of both these authors had oedema of the feet in early infancy, which gradually disappeared.

Grumbach remarked that there is a group of young patients of either sex with a varied number of congenital defects, as described by Ullrich and Turner, in whom testes or ovaries are present normally. In these children gonadal and chromatin sex correspond and normal secondary sexual changes occur at puberty. He suggested that these patients should be grouped under the title of Turner-Ullrich syndrome to differentiate them from those, nearly all female, who also have gonadal atrophy, usually with male sex chromatin, whom he would label simply as gonadal dysgenesis.

As might be expected in a syndrome combining so many different defects, many examples are incomplete. In three of the seven children described here the appearances came to be characteristic of the symmetrical type of the status. The demonstration of cytological male sex in morphological females showed that they belonged to the gonadal dysgenesis group. The oedema present in the other four was identical with that seen in these three. In addition some other of the described features, such as small size or dystrophy of the nails, were usually present, and it is suggested that they are incomplete forms of the status and should be included in the Turner-Ullrich syndrome.

Summary

Seven children, each of whom showed symmetrical peripheral oedema of the lower extremities and usually of the upper extremities to a lesser degree, are described.

Four of them are considered to be examples of the symmetrical type of status Bonnevie-Ullrich in incomplete form, while the remaining three, all girls, are examples of the more complete form, also known as Turner's syndrome or gonadal dysgenesis.

When children show this clinical picture it is advisable to determine the genetic sex by examination of the nuclear chromatin.

Thanks are due to Dr. A. G. Marshall for pathological investigations and to Dr. Alan Booth for radiological examinations.

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PAEDIATRIC PATHOLOGY CLUB

Proceedings of the Fifth Annual Meeting

The Fifth Annual Meeting of the Paediatric Pathology Club was held at Bristol on October 23 and 24, 1959. The meeting on October 23 was held at the Children's Hospital, St. Michael's Hill, when the chair was taken by Dr. Norman Brown. The meeting on October 24 was held at Southmead Hospital, when Dr. Frank Lewis was chairman. Dinner was taken at the Ashton Court Country Club. Forty-five members and guests attended the meeting.

Scientific Communications

EDWARD HALL (Liverpool). 'Primary Hyperoxaluria.' Eight cases of this condition occurring in three families were described and the histology illustrated. The familial nature of the condition was briefly discussed. (Further details of these families are to be published in this journal shortly.)

J. F. BOYD (Introduced by A. M. McDONALD, Glasgow). 'Adrenal Hypoplasia in Siblings.' The first child of healthy parents was admitted when 3 weeks old with a history of abdominal pain and vomiting. Intestinal obstruction was diagnosed and at laparotomy a volvulus of the small intestine was found and was undone successfully. Post-operatively vomiting continued; the patient's condition deteriorated and he died. Autopsy revealed hypoplastic adrenal glands.

The second child born four years later was also a boy and he was admitted when 9 days old with a history of persistent vomiting. No ante-mortem diagnosis was made, but the child was treated on the basis of an overwhelming infection with hydrocortisone and antibiotics. In spite of this his condition deteriorated and he died within 24 hours.

Autopsy revealed hypoplastic adrenal glands.

The paper described and compared the post-mortem and histological features in the two cases. The evidence suggested that in each case this was a primary failure of the adrenal glands rather than a pituitary failure.

AMINASH MITHAL (Introduced by JOHN L. EMERY, Sheffield). 'Postnatal Development of the Lung.' A study of the postnatal development of the terminal respiratory unit had been carried out which indicated that there is an increase in the number of alveoli following birth. There is a rapid increase in the production of alveoli during the first year after birth and a steady increase in the formation of alveoli throughout the whole of childhood.

Differential counts had been done on the respiratory tubes in the lung which suggested that there is an increase after birth in the number of small bronchioles and that slow progressive cartilagization of these bronchioles occurs during later childhood.

P. O. YATES (Introduced by F. A. LANGLEY, Manchester). 'Birth Injury to the Neck.' This paper was published in full in this journal (*Archives of Disease in Childhood*, 34, 436.)

KEITH ROGERS (Birmingham). 'Group F Haemolytic Streptococci as Pathogens in Children.' This group of streptococci is of importance in lesions connected with the whole gastro-intestinal tract, but the organisms demand a slight increase of CO₂ in the atmosphere in which they are grown, and a simple technical procedure was described to provide this.

EDITH FAIERMAN (Introduced by HUGH CAMERON, Birmingham). 'The Significance of One Umbilical Artery.' Eleven cases of single umbilical artery were encountered among 411 routine autopsies on stillbirths and live born babies of 8 weeks of age or less (an incidence of 2.7%).

Severe associated malformations were found in 81%, and in 23% of controls. The commonest malformation was of the lower urinary tract. There was a high incidence of stillbirths (45%) and of twinning (18%). In only one case was there an associated abnormality of the placenta. No correlation was found between the condition and maternal factors.

Absence of an umbilical artery can be diagnosed at birth by simple examination of the cord. In the absence of severe external malformations, such an infant has a 2:1 risk of internal malformations, which may require early surgical treatment.

G. S. ANDERSON (Newcastle). 'Pituitary Lesions Associated with Congenital Adrenal Hypoplasia.' Pituitary malformations in the absence of severe lethal malformations of the head are rare and comprise four published cases, all showing adrenal hypoplasia.

Three further cases were briefly described although one showed a cleft palate and other incidental abnormalities. The three infants died unexpectedly at 18, 23 and 33 hours and in all the adrenals were hypoplastic, resembling those in anencephaly. In one, a male, the pituitary grossly appeared absent but may have been ectopically placed in the sphenoid bone. The testes

were undescended and showed marked tubular and interstitial cell hypoplasia.

In the other two cases, both females, a small bean-shaped nodule of tissue was found in a small sella. Serial sections in both cases showed it to consist solely of pars anterior. In both cases there was a small rounded blunt knob of tissue in the region of the tuber cinereum which histologically was composed of malformed neurohypophyseal tissue anterior to which was a minute island of anterior lobe cells. In one case these cells apparently formed an attenuated connexion with the anterior lobe tissue in the sella.

It was suggested that the fundamental lesion in these cases was the pituitary malformation and that the adrenal hypoplasia was but one effect of this, although probably the most important.

H. B. MARSDEN (Manchester). 'Herpes Encephalitis following Fracture of the Skull.' A girl, aged 4 years, sustained a compound depressed fracture of the skull. There was excellent recovery for one week but on the eighth day pyrexia developed with convulsions and progressive coma. The child died 11 days later and at autopsy an inflammatory reaction was found in the brain involving the meninges and, in particular, the pons and basal ganglia. Perivascular cuffing and foci of inflammatory cells were prominent. An abundant growth of herpes virus in HeLa culture was obtained from the basal ganglia, the lung being sterile.

Evidence was produced to suggest that this was a case of herpes encephalitis, the virus probably entering at the site of the fracture.

The distribution and nature of the lesions were predominantly basal and cellular rather than destructive and unusual. Comment was made on the absence of Lipschütz bodies or type-A inclusions.

K. M. LAURENCE (Cardiff). 'The Pathology of Hydrocephalus.' The material seen between 1955 and 1958 at The Hospital for Sick Children, Great Ormond Street, London, was presented.

On the basis of the series, under-absorption was thought to be unproven, and over-production of C.S.F., seen in cases of choroid plexus papilloma, though interesting, was uncommon, while obstruction to the C.S.F. pathway was both pathologically and numerically the most important. Examples of aqueduct malformation were shown, most of which were found in association with other C.N.S. anomalies, notably spina bifida cystica and the Arnold-Chiari malformation. It was stressed that in cases of spina bifida cystica, the often associated hydrocephalus, although frequently due to malformation, was in many cases aggravated by, if not entirely resulting from, post-inflammatory lesions caused by ascending infection from the myelocoele.

Aqueduct gliosis, although rare, presented problems in aetiology. Because of its association with neurofibromatosis, it was suggested that, like neurofibromatosis, it might be hamartomatous in origin.

The purely inflammatory lesions formed about half the series. The various pathological changes, such as

aqueduct ependymitis leading to aqueduct block, and occlusive fibrosis of the arachnoid resulting in fourth ventricle exit foramen, or basal cistern block occurring singly or in combination, were illustrated by cases.

It was stressed that in over 60% of this group bleeding into the C.S.F. pathway at the time of delivery was regarded as the aetiological inflammatory agent, though in some cases little evidence of bleeding could be found at the time of the autopsy. (In discussion several members said that this series is a highly selected group and does not represent the hydrocephalus seen generally in the country.)

H. URICH (London). 'Some Remarks on the Neuronal Lipidoses.' All neuronal lipidoses share the characteristic feature of accumulation of lipids in the cytoplasm of nerve cells in addition to storage in other organs. Six diseases of this group were studied in Dr. R. M. Norman's laboratory in Bristol (see Table). Contrary to some of the older teaching based on superficial similarities, these diseases constitute separate entities distinguishable both histologically and by chemical analysis.

The conditions most commonly confused are Tay-Sachs' disease and Niemann-Pick's disease, despite the differences in the chemical composition of the brain in the two conditions. Examination of a case of Tay-Sachs' disease with exceptionally severe visceral involvement also revealed histological differences. The coarse vacuoles found in this case in reticulo-endothelial and glandular epithelial cells were apparently empty in formalin-fixed material, while in Niemann-Pick's disease the stored lipid could be easily stained with haematoxylin lakes.

Batten's disease (juvenile amaurotic idiocy) differs from Tay-Sachs' disease in the absence of an excess of ganglioside in the brain. The lipid stored in reticulo-endothelial cells of some cases is histochemically similar to that found in the neurones. It has not been identified chemically.

Gargoylism can be distinguished from the amaurotic idiocies by the involvement of connective tissues including the meninges and the adventitia of cerebral blood vessels.

In infantile Gaucher's disease only a few nerve cells show unequivocal signs of storage while others undergo degeneration without preceding storage. This phenomenon also occurs in other neuronal lipidoses and may be illustrated by the atrophy of the granular layer of the cerebellar cortex in Batten's disease.

The inclusion of metachromatic leuco-encephalopathy in this group is based on the finding of storage of sulphatide in numerous neurones of the basal ganglia, brain stem, spinal cord and posterior root ganglia. Severe demyelination, which is the most striking feature of this condition, may also be found in other neuronal lipidoses, particularly in cases of Tay-Sachs' disease with a protracted clinical course.

Neuronal storage, degeneration of nerve cells and loss of myelin sheaths may all be interpreted as results of the various disorders of lipid metabolism, presumably enzyme deficiencies, characteristic of these diseases.

THE NEURONAL LIPIDOSES

	Localization of Storage		Predominant Stored Substance	
	Neuronal	Visceral	Neuronal	Visceral
Tay-Sachs' disease	Ubiquitous	(Glandular parenchyma R.E. system)	Ganglioside	? (Polysaccharide)
Niemann-Pick's disease	Ubiquitous	R.E. system, glandular parenchyma	Sphingomyelin	Sphingomyelin
Batten's disease	Widespread	(R.E. system)	?	?
Gargoylism	Widespread	Connective tissue, glandular parenchyma R.E. system	?	Polysaccharide
Infantile Gaucher's disease	Minimal	R.E. system	?	Cerebroside
Metachromatic leuco-encephalopathy	Limited	Kidney, bile passages	Sulphatide	Sulphatide

R. M. NORMAN (Bristol). 'Intracerebral Calcifications.' The histological evidence pointing to a vascular factor in the pathogenesis of cerebral calcification was illustrated by reference to cases of the Sturge-Weber syndrome and of symmetrical cerebral calcification. In the former condition the calcifications tend to be localized in the outer layers of the cortex, that is, near the meningeal angiomas, but they are also seen in certain deeper laminae, notably the fourth layer of the calcarine cortex. In symmetrical cerebral calcification, whether associated with parathyroid deficiency or with familial microcephaly, the cortical calcifications have a predilection for the deeper parts of the gyral walls, especially in the boundary zones between major arterial territories. The fourth layer of the calcarine cortex may also be selectively affected. In the basal ganglia the localization of the calcifications is very similar to that found in status marmoratus following birth injury, though the lesions are otherwise dissimilar. The common factor appears to be a selective vulnerability of the capillaries of the affected areas.

The following short papers and cases were also presented:

KENNETH RHANEY (Dundee). 'Hypertrophy of the Choroid Plexus.' A full-term female foetus with gross hydrocephalus was delivered with difficulty after craniotomy. The trunk and limbs were normally developed and nothing of interest was found in the thoracic and abdominal viscera.

The head was greatly enlarged although the bones of the vault showed premature synostosis and the fontanelles were not enlarged. Reconstruction of the damaged brain showed that the septum lucidum, fornix and most of the corpus callosum were absent and that the lateral and third ventricles formed a single chamber. The lateral ventricles were greatly dilated; they were enclosed by a thin shell of cortex and atrophic white matter and theependymal surface was coarsely nodular. Posterior to the genu the corpus callosum was replaced by a thin membrane which lined a large sac. This sac lay between the cerebral hemispheres posteriorly and formed part of the common ventricle.

The whole choroid plexus in the common ventricle

formed a large tumour with a rough irregular surface. On histological examination it showed the classical structure of a simple choroid papilloma.

The brain stem and cerebellum showed no abnormality. The aqueduct was of normal size, and the foramina of the fourth ventricle were patent. The leptomeninges showed recent haemorrhage but no other macroscopic abnormality.

The papillomatous choroid plexus appeared to be responsible for ventricular dilatation. It may well have produced an excess of cerebrospinal fluid and also given rise to obstruction.

LESLIE WHITE (Manchester). 'Cushing Syndrome associated with Suprasellar Tumour in an Infant.' A male infant of 3 months presented with typical Cushing syndrome. There was sudden deterioration after 17 days with death. Autopsy revealed a large suprasellar tumour and bilateral adrenal hypoplasia with terminal thrombosis of the galenic veins. The tumour, which was continuous with a normal size pituitary gland, had an undifferentiated lobular epithelial structure. Some evidence of basophil cell origin was obtained.

A. M. McDONALD (Glasgow). 'Krabbe Type Diffuse Cerebral Sclerosis.' A female, aged 9 months, was admitted the day before death severely ill with bronchopneumonia; she had been brownish-yellow at birth and for the following two months. At 7 months of age she had not sat up; she was a fat, mentally deficient child and her eyes did not follow light. Skull circumference was 43 cm., and she had a large anterior fontanelle.

At autopsy a Krabbe type of diffuse cerebral sclerosis, bronchopneumonia, gastric ulcers and oesophagitis were found.

A. M. McDONALD (Glasgow). 'Congenital Absence of Biliary Ducts.' A premature male baby with complete harelip and cleft palate developed jaundice and white stools at the age of 7 weeks. Liver function tests suggested an obstructive type of jaundice.

A cholangiogram showed free passage of contrast medium into the duodenum through the common bile duct. The hepatic duct was faintly outlined and small in calibre.

At biopsy the liver was olive green. Histological examination showed that biliary ducts were either absent or in very small numbers. Biliary thrombi were also in small numbers. Early fibrosis was equivocal. The lesion was considered to be a bile duct atresia at the ductal level and it was thought that cirrhosis would follow.

The child is now 10 months old, is very well and not jaundiced. The cleft palate is about to be repaired.

E. HALL (Liverpool). 'Ganglioneuroblastoma. An Unusual Presentation.' A case of extra-adrenal abdominal ganglioneuroblastoma in a 2½-year-old boy who presented with severe diarrhoea and some vomiting. There was a striking cessation of symptoms after removal of the tumour. Attention was drawn to a small number of similar cases recorded in the literature, and the possibility that a minority of these tumours may have internal secretory effects was discussed.

IAN DAWSON (London). 'Adenocarcinoma of the Testis in a Child of 11 months.' A Jewish child of 11 months developed a gradual, apparently painless swelling in the left testis over a period of two months. Both testes were present in the scrotum. A left orchidectomy was performed.

The testes measured 3×2×1.5 cm. and appeared completely replaced by yellowish, rather gelatinous tissue. The epididymis appeared to be intact.

The histological appearances were uniform throughout all the blocks. The tumour consisted of irregularly arranged gland acini which varied in size from small solid elements to irregular spaces, into some of which papillary processes projected. The epithelium was in places cubical, in places low columnar. The acini were separated by loose oedematous stroma.

This tumour falls into the group of those described by Magner (1956) and may be called an adenocarcinoma of infant testis. The source of the growth remains uncertain but may be rete or junctional tubules.

(Several members of the club had seen similar tumours.)

R. L. HOLMAN (Introduced by G. OSBORN). 'Persistence and Overgrowth of Immature Blastema in Both Kidneys of a Premature Infant.' A female infant born of 32 weeks gestation who survived 13 hours. Death was due to respiratory insufficiency; the lungs were only partially expanded and haemorrhagic.

Both kidneys were greatly enlarged; each weighed 70 g. and measured 7.0×3.5×3.5 cm.; the cut surfaces showed replacement of normal structure by irregular cream and brown areas. The capsular surface showed a moderate degree of lobulation.

Microscopically both kidneys showed widespread persistence and overgrowth of immature blastema tissue

interspersed and mingled with smaller zones of normally differentiated renal tissue. Immature blastema showed all gradations from undifferentiated deeply basophilic round cells through developing tubules and glomeruli to moderately well defined structures. A moderate number of mitoses were present in many such areas. There were many large straight tubules, probably all collecting tubules, extending radially from the medulla through the immature cortical zone almost to the capsule. Many of these were dilated, especially where they branched. Some collecting tubules ended in relation to zones of immature blastema tissue. Terminal collecting ducts were largely of normal appearance and lined by transitional cells distended with glycogen. No heterotopic tissues such as skeletal muscle and cartilage were found.

The diffuse nature of the anomaly in these kidneys suggests some generalized failure of organization of normal development rather than a localized overgrowth of metanephric blastema, such as occurs in a nephroblastoma.

HUGH CAMERON (Birmingham). 'Angioma of Larynx in Laryngeal Stridor.' This paper concerned three infants with severe persistent laryngeal stridor which did not respond to medical treatment or tracheotomy. All showed severe laryngo-tracheitis at autopsy and a small submucosal capillary haemangioma of the sub-glottis. These angiomas may be missed unless particularly careful examination is carried out and they appear to be more common in intractable laryngeal stridor than is usually recognized.

DOUGLAS BAIN (Edinburgh). 'Congenital Leukaemia.' Two cases of congenital leukaemia were described, one of which was presented at birth with nodules in the skin. There was no history of mongolism or of radiation during pregnancy.

JOHN L. EMERY (Sheffield). 'Chronic Rectal Ulcer in Boy of 14.' A chronic indurated bleeding ulcer situated in the anterior wall of the rectum which was probably basically an angioma.

G. S. ANDERSON (Newcastle). 'Pinhole Perforation of the Foetal Colon.' A child with meconium peritonitis due to perforation of the colon, apparently due to a local defect in musculature.

A. M. McDONALD (Glasgow). 'Umbilical Polyp.' An 11-month-old male infant presenting with an umbilical polyp. Since the cord separated a small black lump had been present in the umbilicus. Histology showed the features of a simple pigmented naevus, the colour being due to excessive melanin.

BOOK REVIEWS

Helping Your Child to Get Well. Ed. LEN CHALONER.

By SIMON YUDKIN, J. LANGRIDGE, PHYLLIS WOOLRICH and LEN CHALONER. (Pp. 142; 31 figs. 16s.) London: Allen & Unwin. 1959.

This book is full of sound common sense. It is not intended to be a family doctor but information on some diseases is given for which the child would be nursed at home. It is in three parts. The first deals with observation and the nursing of sick children at home. It is written in such a way that it makes for a good patient-doctor relationship. The second part gives good advice on providing interests for children of all ages who are confined to bed. The suggestions are useful and inexpensive. The third part discusses the problems arising when a child has to go into hospital. The book can be highly recommended but it seems a pity that the price is so high.

The Child with a Handicap. Edited by EDGAR E. MARTMER. (Pp. xxiv+409; illustrated; 82s. 6d.) Oxford: Blackwell Scientific Publications. 1959.

Although the preface states that this book 'is not primarily a medical text' but is designed for 'a more general public', there is much in it to profit family doctors, school doctors and paediatricians.

The main part of the book is composed of 15 chapters contributed by individual experts on all the usually accepted childhood handicaps, poliomyelitis, cerebral palsy, visual defects, speech and hearing defects, muscular dystrophy, mongolism, as well as some of the less common handicaps such as familial dysautonomia and amputations.

Each of these chapters is a clearly written guide to the background and clinical definition of a specific handicap. The effects of the handicap are explained and treatment as well as general management of the child are detailed. Special note is made of the various agencies concerned in medical and surgical care, physiotherapy, schooling, occupational training and guidance in choosing a career.

Five of the chapters are illustrated and most contain references to recent work, especially to recent articles in paediatric literature.

The first five chapters are separate essays, defining the part played by the members of 'The Team' in the management of the disabled child. The points of view of the parent, the physician, the psychiatrist, the teacher, and the social worker are given equal prominence.

A chapter on the Role of Adoption Agencies is somewhat unexpected in a book of this sort, but makes clear the readiness of would-be adopting parents in the United States to accept children with a variety of handicaps.

The following chapter on Heredity Counselling gives examples of family situations in which such discussion had been very important.

The final chapters are a series of short guides. Besides lists of play, reading and education materials, they include in 'Guides for Discipline' and 'Guides for Parents' two short, thoughtful essays on the general management of any disabled child.

Although the book has 27 contributors, the Editor has been successful in obtaining a high level of clarity in the descriptions of the various disabilities, of modern methods of management, and of the many agencies involved.

Whilst some of the chapters are directed chiefly to the parents of handicapped children, much of the clinical detail would seem, to a reviewer working in the British Isles, to be far beyond the requirements of the average parent. The book's principal value lies in its wide view of the whole field of handicapped children and its very clear presentation of the details of so many disabilities. It should be read by all who have any part in the clinical, educational or administrative care of any child with a handicap.

Diagnosis of Congenital Heart Disease, 2nd ed. By SWEN R. KJELLBERG, EDGAR MANNHEIMER, ULF RUDKE and BENGT JONSSON. (Pp. xiv+866; 727 figs. \$28.00) Chicago: The Year Book Publishers, Inc. 1959.

The second edition of this important diagnostic manual of congenital heart disease closely follows the pattern of the first and is based on a detailed analysis of material seen at the Karolinska Hospital in Stockholm, now swollen to 742 cases. It is enlarged by four chapters, contains many amplifications and corrections as well as an increased number of illustrations.

In the 30 different abnormalities studied, six contain between 60 and 140 examples of each and between them comprise 80% of the total. They are patent ductus arteriosus, ventricular septal defect, coarctation, pulmonary stenosis, auricular septal defect and Fallot's tetralogy, in that order of frequency.

The first few chapters are devoted to the embryology of the heart, X-ray anatomy, techniques and to a brief summary of material to be studied. Thereafter each condition is taken in turn and the chapters follow each other in a repetitive pattern of clinical features and E.C.G., X-ray, electrokymography, cardiac catheterization, haemodynamics during exercise and angiocardiology. This list may be abbreviated for a few uncommon conditions but the arrangement never alters. Each condition is illustrated with a profusion of photographs, diagrams, tracings and charts. At the end of the

book there is a list of over 700 references with titles in full and an index which, though short, appears to function efficiently.

To the reviewer, an English-style consulting paediatrician without special cardiac training, of average intelligence but perhaps with difficulties regarding spatial relationships, this book is a revelation and has led to a revolution in the understanding of congenital cardiac disease. Every page and illustration bears evidence of imaginative effort spent in clarifying and elucidating problems relating to the action and haemodynamics of the heart working under abnormal conditions, and step by step each investigation is made to yield up its logical contribution to diagnosis. An important contributory factor to the character of this book is the impeccably simple and consequently lucid English in which it is written, which must reflect on both the original Swedish and on the translation.

The book sticks precisely to its terms of reference and diagnosis never spills over into prognosis, nor is there ever a hint that the subtle exposition of morbid anatomy, physiology and haemodynamics might have a bearing on treatment. But perhaps it would be greedy to ask for more: it is a fine book to have to refer to frequently.

Rheumatic Fever: Epidemiology and Prevention. Ed. R. CRUICKSHANK and A. A. GLYNN. (Pp. 193; 26 figs. 25s.) Oxford: Blackwell Scientific Publ. 1959.

In September, 1956, at the invitation of Professor R. Debré a conference was held at the International Children's Centre in Paris under the chairmanship of Dr. David Rutstein.

Experts from all over the world assembled to discuss the epidemiology and prevention of rheumatic fever. This record of the proceedings is arranged in sections, each of which is introduced by an acknowledged authority (R. Wahl, P. Hedlund, M. McCarty, E. G. L. Bywaters, M. Finland, P. Mozziconacci and Mlle J. Labesse), and each is followed by a series of short communications and a general discussion. Among a large number of distinguished delegates Bruce Perry, R. E. O. Williams and R. Cruickshank represented Great Britain.

This account contains a cross section of international opinion regarding the bacteriology and immunology of Group A haemolytic streptococci, including practical information about the isolation and recognition of these organisms and their antibodies. This is followed by a discussion of the epidemiology of streptococcal infections and their relationship to the development of rheumatic fever in certain individuals. This leads naturally to consideration of methods of preventing rheumatic fever.

After an interesting discussion by Finland on changes in the resistance of bacteria to antibiotics since 1949, a number of important points were raised. For example, although sulphonamides are suitable for prophylaxis of rheumatic fever since they are not bactericidal, they are quite unsuitable for treatment of streptococcal infections or for the prevention of first attacks. Penicillin is the most effective available agent, both for prevention and control of streptococcal infection. Unfortunately half

the attacks of rheumatic fever occur without any obvious sore throat and the diagnosis of rheumatic fever is still largely a matter of clinical judgment and application of the criteria laid down by Duckett Jones.

The proceedings of the Conference have been translated and edited by Professor R. Cruickshank and Dr. A. A. Glynn, who are successful in producing a readable and well balanced book.

The Artificial Feeding of Normal Infants. By WILLIAM EMDIN. (Pp. 113; 3 figs. 16s.) Howard Timmins. 1959.

It is not very long since the artificial feeding of infants was considered an exact science and books on the subject were bulky and their formulae complicated. As a result few students made any serious attempt to understand the problem and many practitioners have been content to leave it to their nursing associates or advised mothers to follow the instructions on the tin.

Since then the subject has been simplified and it is realized that most babies are very tolerant and will survive on almost anything approaching a normal feed. There can be no scientific exactitude in a subject where measurements are in teaspoons which from house to house vary in size and in how well they are filled.

A new difficulty has arisen, however, in the multiplicity of preparations now available for infant feeding and this book sets out to present 'a simple, practical feeding scheme applicable to feeding with natural cows' milk and all types of the proprietary milk products in common use'. In this it succeeds admirably and the principles laid down are those generally recognized by paediatricians as the most satisfactory.

The book is divided into three parts. The first considers artificial feeding in general, the second describes the use of the different preparations available, and the last is an up to date discussion on mixed feeding and the use of dietary supplements. The subject matter is clearly and simply presented and there are numerous valuable tables making for easy reference.

This is a most satisfactory book and one which I have no hesitation in recommending to students, nurses and practitioners.

A Manual of Paediatrics for South-East Asia. Edited by PINCHAS ROBINSON and ARVID WALLGREN. (Pp. xlx+464. Rs. 7.50.) Calcutta: Orient Longmans. 1959.

Although half the world's children live in the tropics and sub-tropics, the study of disease problems among them has been slow to gather momentum. Now, however, things are changing, and tropical paediatrics is becoming recognized as a subject worthy of world-wide study. Courses are being held, Chairs established, a journal is now flourishing, and finally the text-books have appeared.

This is the second book to have been published within the last two years, with two distinguished editors and 55

contributors. The editors criticize the first book on grounds of expense, and this book is a courageous attempt to reduce cost by the 'economy' standard of its production, and by virtually abolishing illustrations.

Such an attempt, however, is bound to be fraught with difficulties, and it must be confessed that this is rather an odd book. Its 440 pages of text are subdivided into a very large number of small essays with no attempt at grouping under common headings by system. The result is a volume, more readable than most text-books, but disconcertingly haphazard for the undergraduate at whom it is largely aimed. One feels that a little co-ordination and fusion of the many separate sections would produce a much more coherent book.

The question of format, however, is less important than that of content and balance, and this is where the book is most open to criticisms. A few instances will suffice. The section on rare muscular disorders is given almost as much space as the whole of the respiratory tract; coeliac disease and fibrocystic disease of the pancreas are together granted only half a page; and, surely, in a book designed to cover tropical paediatrics, there is something wrong when kwashiorkor is dismissed in one page, and the whole of infant feeding, nutritional disorders and vitamin deficiencies are given less space than the much rarer disorders of the endocrine glands. Whilst, too, it is quite legitimate, though perhaps unwise, to dispense with illustrations in a book of this sort, one wonders what purpose is served by including 13 only, four of them on one disease.

Taken individually, many of the sections are admirable. But the preface states the aim of the book as one 'which covers all or most aspects of child care as those appear in this part of the world, which includes the total field of paediatrics as taught in the West, and many other problems which are of little or no importance there'. This would be a very large claim for a much larger book, and is far from being realized here.

In its present form it is difficult to recommend this book as the sole paediatric text-book for undergraduates. But if in future editions the editors would expand those parts dealing with the tropical and preventive aspects, especially as they apply to South-East Asia, and reduce somewhat those sections on general paediatrics which are dealt with more fully in other books, the book would establish itself as a useful and interesting companion to a new and important subject.

Le Bien-Etre de L'Enfant en Afrique au Sud du Sahara.

By MAURICE GAUD. (Pp. 186.) Published by the Centre International de L'enfance, Lagos. 1959.

The publication commemorates and, to some extent, reports the proceedings of a six-day congress covering an immense field which was held in Lagos in March, 1959, under the Chairmanship of Professor Robert Debré. Delegates from European countries with African interests joined representatives from the territories themselves, the majority of whom held some administrative post. The participants are categorized

in the preface as sociologists, ethnologists, agronomists, psychologists, physical anthropologists, educators and specialists—in public health, sanitary education, growth, and juvenile delinquency. There were also observers from a number of political organizations. Scientific communications seem to have been concerned with correspondingly diffuse subject matter, without much integration, although the abstracts (in French and English) are too brief to provide much more than main headings. Valuable as this volume should prove as a memento for those fortunate enough to have attended the congress, it is unlikely to be of profit to a wider public, unless perhaps for the useful bibliography that concludes it.

Le Nouveau-né—Directives Therapeutiques Medico-chirurgicales. By MARCEL FÉVRE. (Pp. 190; Fr. fr. 2,500.) Paris: G. Doin et Cie. 1959.

This book is written for children's physicians by a surgeon, with the intention of showing them the indications for surgical intervention in the newborn. The author is professor of paediatric and orthopaedic surgery in the faculty of medicine in Paris and has already written a book about paediatric surgery for surgeons.

It is obvious on reading the book that he is a surgeon of wide experience and considerable skill. He keeps admirably to his self-imposed limits and does not discuss details of technique of no interest to physicians. The chapters cover conditions requiring immediate treatment, birth injuries, visible congenital defects, internal congenital defects, disorders of the post natal period and resuscitation. A wide range of conditions is covered in considerable detail. The methods described are modern and in most cases similar to those used in Britain; the chapter on intestinal obstruction is particularly good. The chief defect in the book is the lack of illustrations, necessary for the rare conditions described. There are a few adequate diagrams and a handful of very bad photographs. The book is paper-backed and uncut. The type used is admirable and there is a good index. The author deliberately limits his references to 18 standard works, although he names many more authors in the text (including 'Grey and Turner'!).

This is a good and unusual book which requires little knowledge of the French language and will provide all paediatric physicians with a good deal of new information.

Paediatric Tutorials: The Newly Born Infant. By

ANDREW BOGDAN. (Pp. 38; 3s.) Available from Anstick's Medical Bookshop, 53 Great George Street, Leeds 1, and other medical bookshops.

Dr. Bogdan has constructed a small notebook to be used at the cot-side. The main headings are filled in which deal with the normal and sick infant and ample blank pages are included for the student to make his own notes.

Skeletal Calcification and Phosphate Metabolism. By R. STEENDUK. (Pp. 163; 510 refs.) M.D. Thesis, Handels Drukerij J. Ruyendaal, Amsterdam.

The metabolic processes responsible for skeletal calcification revolve around the problems of calcium and phosphorus absorption and excretion, and the maintenance of the levels of these substances in the blood. The unravelling of these problems has always advanced as much by the study of rickets as from a direct study of ossification in healthy bone. This monograph, a university M.D. thesis, summarizes the modern concepts of these processes against an exhaustive and critical review of the literature (some 500 references are listed) supported by the author's own clinical and experimental observations in cases of primary resistant rickets and of the de Toni-Fanconi syndrome. The observations were designed to elucidate specific points regarding calcium metabolism and serum phosphate regulation and tubular reabsorption, around which so much that concerns bone formation appears to revolve.

In the first few sections the author traces the radical changes that have come over our ideas on the mineralization of ostioid; how the older ideas of precipitation from a supersaturated solution of minerals, and the importance of phosphatase, have become outdated and given place to the idea of crystallization of hydroxy-apatite of calcium on to an organic, preformed, mucoprotein template.

The rest of the monograph discusses extensively the biochemical and clinical aspects of the activity of vitamin D in relation to rickets, the extremely complex relationships that exist between calcium, phosphate, the renal excretion and retention of these two substances, the actions of vitamin D and parathyroid, and the rate of both calcification and the removal of mineral salts from bone.

With regard to the role of the renal tubules in the production of resistant rickets, whether primary or in association with amino-aciduria and glycosuria, he discards the theory of a phosphate diabetes, a primary failure of reabsorption of phosphate by the renal tubules as too simple and even misleading, and suggests that there is a failure at some point in the metabolic merry-go-round in which an equilibrium is normally maintained between (1) the availability of minerals for calcification; (2) the rate of calcification; (3) the serum phosphorus level; (4) the tubular reabsorption of phosphate; and (5) the solubility of bone salt. He considers that clinically the availability of calcium is probably the main conditioning factor in this equilibrium.

In the introduction the author complains, perhaps rightly, that clinicians are comparatively ignorant of the physiology of calcium and phosphorus metabolism, and he quotes Howard as stating that 'in the field of modern medical investigation, the clinician usually is placed at the bottom of the totem pole, beneath his colleagues versed in the basic science . . . though his opportunities for viewing the subject in its broadest sense are apt to be greater than those of the biochemists or physicists'.

Anyone willing and still able, for it is tough going, to spend a long week-end reading and digesting this monograph will find his grasp of the complications of calcium

and phosphorus metabolism brought firmly up to date, and the boundaries of his biological thinking considerably widened.

Involution of the Ductus Arteriosus. A Morphological and Experimental Study, with a Critical Review of the Literature. By A. SCIACCA and M. CONDORELLI. (Pp. 52; 25 figures. Sw. fr. 7.00.) Basel and New York: S. Karger. 1960.

This treatise first gives a critical review of the literature on the theories of the closure of the ductus arteriosus. There are some valid criticisms of the views of Barcroft and his colleagues; no mention is made of the work of Patten (1933), whose conclusions were the same as the authors'; and the more recent contributions of Adams and Lind (1957) and Dawes and his colleagues (1954) to our knowledge of the physiology of the foetal and neonatal circulation are not discussed.

There follows a description of the authors' morphological and experimental studies of the time of closure of the ductus in guinea pigs, which includes the effect of sudden interruption of the blood flow through the ductus and the pulmonary artery in the foetus and newly born animal, and also some angiocardigraphic studies. Their findings support those of Patten and point to a gradual development of the circulation through the lungs during foetal life, the pulmonary flow increasing as the ductal flow decreases. No light is thrown on the exact mechanism of closure of the ductus, but the authors believe it to be a gradual process.

There are interesting observations of the varying size of the ductus relative to the pulmonary artery at different stages of foetal development which may be significant in relation to differences in size and shape of patent ducts found in infants and children at operation and may give a clue to the time of a possible foetal insult responsible for the condition.

The study will be of particular interest to cardiologists and also to pathologists, physiologists and anatomists interested in this field.

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Catalog of the Clifford G. Grulee Collection on Pediatrics. Edited by HERMAN H. HENKLE. (Pp. viii+340. \$15.00.) Chicago: The John Crerar Library. 1959.

This book is beautifully produced and refers to Grulee's collection of over 4,000 publications which were given to the John Crerar Library in Chicago.

Anyone interested may consult the book in the library of the B.M.A.

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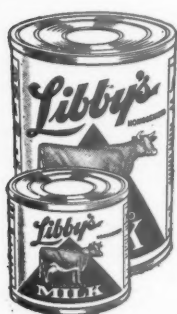
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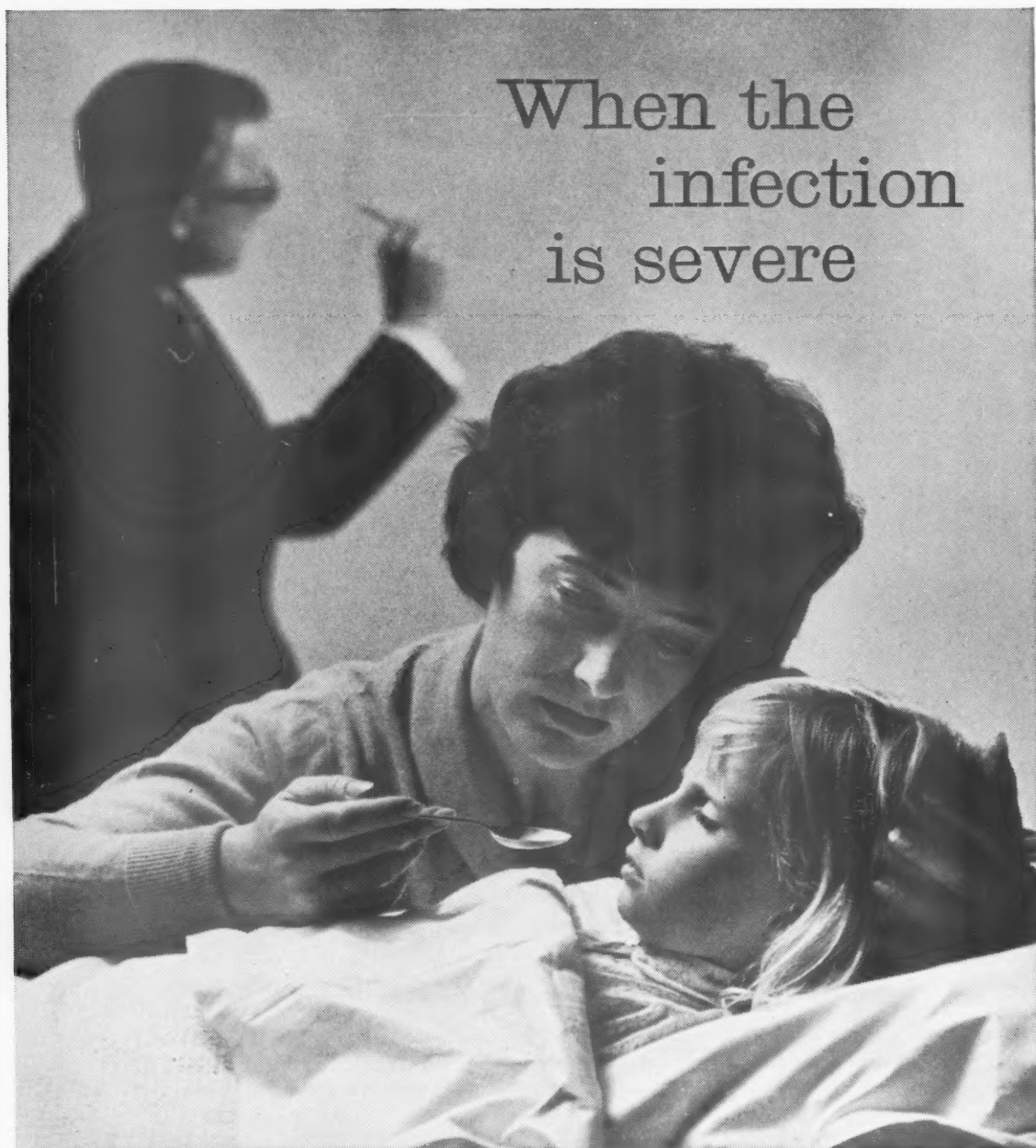
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